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Research Article

Clinical Profile of Hospitalized Community Acquired Childhood Pneumonia in Dhaka, Bangladesh

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Abstract

Introduction: The 2 major bacterial causes of childhood pneumonia are *Hemophilus influenzae* type b (Hib) and *Streptococcus pneumonia* (SPN). The objective of this study was to describe clinical profile of hospitalized CAP cases in children in a Low Middle Income Country (LMIC) and compare to practices in High Income Countries (HIC). The goal was to justify maternal immunization during pregnancy.

Methods: Medical records of patients admitted between March' 2014 and August' 2014 were reviewed. 219 cases were identified with lower respiratory tract diseases, among which 83 were diagnosed as bacterial CAP and enrolled into this study. Intercooled stata" version 8.0 was used for statistical analyses.

Result: Mean age for male was 5.9 months and for female was 11.7 months; mean weight for male was 5.8 kilograms and for female was 6.5 kilograms. Eighty-nine percent of this population was under 12 months, 69 percent was under 6 months and 22 percent was under 2 months of age. Infants under 6 months were more likely to be tachypneic (p=0.04) and hypoxic (p=0.05) when compared to infants and children over 6 months of age. Younger infants under 2 months were even more likely to be tachypneic (p= 0.002) but less likely wheezing (p=0.001) when compared to infants over 2 months of age. Infants under 2 months were 14x at higher risk (Odds ratio [OR]) (p=0.002) for tachypnea. Infants under 6 months were 3x at higher risk (OR) for tachypnea (p=0.02) and hypoxia (p=0.03) when compared to infants and children over 6 months of age. Underweight (< 3rd percentile for age) children were (p=0.01) 2.4 times (OR) more likely to be in respiratory distress than children with normal weight.

Conclusion: Prevalence of vaccine preventable CAP is common under 12 months of age. Maternal immunization during pregnancy with *SPN* and *Hib* vaccines is deemed to be justifiable and a cost effective strategy for community acquired childhood pneumonia prevention in LMIC.

Keywords: Hospitalized childhood pneumonia; LMIC and HIC; Maternal immunization

Introduction

Even as child deaths have declined globally over the last two decades from 12.6 million to 6.6 million, CAP has remained the world's leading cause of death among children under the age of 5 [1,2]. Bangladesh has been determined to be among the countries where 44 percent of the world's children less than 5 years of age live. The highest incidence rate of CAP cases for children less than 5 years is reported at 0.51 episodes/ child-year in Bangladesh [3]. CAP accounted for twenty-six percent of neonatal deaths leading to high Infant Mortality Rate (IMR) in Bangladesh (52.5 vs 6.8/ 1,000 infant births in the US). Of all identified cases, an estimated ten percent require hospitalization [4,5].

In resource-limited settings, risk factors accounting for high childhood CAP-related deaths may include malnutrition, lower socioeconomic status, indoor air pollution (smoking, overcrowding), poor quality drinking water, lack of exclusive breast feeding, immunodeficiency conditions including HIV infection and other viral infections such as measles [3, 6-11]. Potential barriers to optimal prevention and treatment of CAP in Low and Middle Income Countries (LMIC) may include a lack of or access to preventive health care services, including many routine childhood vaccinations; a lack of health education and awareness; complexities associated with diagnostic and treatment modalities; high cost of treatment and most importantly lack of a follow-up care. The lack of a follow-up care results in a post-hospital discharge mortality exceeding in-hospital mortality [12-14] and most reportedly occur at home. This finding may suggest that the mortality incidence as reported in literature may be under-represented. Severe anemia in particular, has specifically been predicted to account for higher post-hospital discharge mortality in children [15].

The two major bacterial causes of childhood CAP in children are *Hemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* (SPN). While effective vaccines are available for these infectious diseases, the earliest age for a routine vaccination, per the WHO schedule, is six weeks in LMIC; unfortunately a disproportionate number of infants die before they are immunized.

There are no data analyzing detailed clinical profiles of severe childhood CAP in hospitalized patients from an inner city hospital in Dhaka, Bangladesh. Thus, the main objective of our study was to portray precisely the clinical characteristics of all childhood CAP cases, particularly neonatal pneumonia cases. The intent was to identify disparities in management and follow-up care of these cases when compared to standard of care practices in High Income Countries (HIC). The primary goal was to increase awareness among clinicians and policy makers in LMIC about these disparities so that the issues may be acknowledged and addressed appropriately. We thus set out to collect detailed data on all childhood CAP cases who were admitted to an inpatient unit at Shaheed Suhrawardy Medical College (SSMC) in Dhaka, Bangladesh over a specific period of time.

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Methods

Data were collected retrospectively from review of medical records of a cohort of patients admitted to a pediatric inpatient unit at SSMC between March 2014 and August 2014. All patients admitted to the pediatric unit are documented in a register with their diagnoses, according to hospital policies. Study was initiated in December 2014. Two hundred and nineteen cases were identified as having lower respiratory tract diseases (pneumonia, bronchiolitis, asthma, pulmonary tuberculosis); of these cases, eighty-three were diagnosed as bacterial pneumonia and documented in their charts by the attending physicians and enrolled into this study.

Those eighty-three paper charts were pulled out from the medical records and reviewed. Pertinent information was obtained from the medical records and noted on excel spreadsheets. Patients were de-identified using codes. Outcome of interests included: 1) clinical profile of the hospitalized childhood CAP cases stratified by age groups and nutrition status and 2) differences in the management, treatment and follow -up care of the hospitalized study cases contrasted with standard of care practices of hospitalized severe CAP cases in HIC.

Clinical profile data collected included patient demographics (age in months and gender) and clinical symptoms/signs. Symptoms included patient or parental/legal guardian's report of fever, cough and breathing difficulties; signs included weight in kilogram, vital signs (respiratory rate, heart rate, and temperature in Fahrenheit [F]) and physical examination findings (crepitation or crackle, wheezing, retraction [use of accessory muscle] and evidence of hypoxia); results of laboratory and imaging procedures (chest x-ray) were also noted. Treatment administered (oral, IntraVenous [IV], or combination [oral + IV] antibiotics) and duration of therapy were documented.

Weight percentiles for age and gender were calculated using the Center for Disease Control (CDC) Children Growth Chart Calculator: 2-20 Years, and the CDC Infant Growth Chart Calculator: 0-3 Years. Malnutrition was defined as weight less than 3rd percentile for age and gender; fever was defined as temperature greater than or equal to 100.4 degrees F; According to World Health Organization (WHO) definition, tachypnea was defined as respiratory rate >40per minute in children >12 months, >50 per minute in infants 2-12 months and >60 per minute in infants <2 months of age; hypoxia was defined as oxygen saturation less than 95 percent on room air (WHO). All data were entered into excel spreadsheets. Statistical analyses were performed using "intercooled stata" version 8.0. The proportion of infants and children demonstrating symptoms and signs consistent with a diagnosis of clinical pneumonia stratified by age groups and nutrition status were compared by a two-tailed Fisher's exact test. Continuous variables (age in months, weight in kilograms) between gender groups were analyzed using a two-tailed t-test. Comparison of risk assessment for respiratory distress (tachypnea, hypoxia and wheezing) between age groups (<12 months versus >12 months, <6 months versus >6 months, and <2 months versus >2 months) and by nutrition status were assessed by Odds Ratio (OR). The analyses and interpretation of data were performed by the authors with the assistance of the Biostatistics Core at Meharry Medical College. Differences in management and follow-up care of the study cases compared to standard of care practices in HIC were analyzed.

Results

Of the eighty-three infants and children enrolled in the study; fifty-six were male and twenty-seven were female with age ranging from 0.5 to 207 months. Eighty-nine percent (74 of 83) of this population was younger than 12 months, sixty-nine percent (57 of 83) was under 6 months and twenty-two percent (18 of 83) was under 2 months of age.

The mean age for males was 5.9 months (range: 0.7-72) and for females was 11.8 months (range, 0.5-120); the mean weight for males was 5.8 kilograms (range: 2.8-14) and for females was 6.5 kilograms (range: 2.3-24). Based on history (parental reporting), infants under than 6 months of age were noted to have a higher frequency (p=0.03) of breathing difficulty when compared to infants and children over 6 months of age; conversely, older children (mean age 29.5 months) were noted to have a higher frequency (p=0.03) of nasal flaring on physical examination when compared to their younger counterparts (mean age 7 months).

As shown in table 1, infants under 6 months were more likely to be tachypneic (p=0.04) and hypoxic (p=0.05) when compared to infants and children over 6 months of age. Younger infants under 2 months were even more likely to be tachypneic (p= 0.002) but less likely wheezing (p=0.001) when compared to infants over 2 months of age. As shown in table 2, risk for respiratory distress among different age groups showed that infants under 2 months were at a 14x greater risk (p=0.002) for tachypnea but at lower risk for wheezing (p=0.001) when compared to infants and children over 2 months of age; infants under 6 months were at a 3x greater risk for tachypnea (p=0.02) and hypoxia (p=0.03) when compared to infants and children over 6 months of age. Fifty percent of the patients were underweight (less than third percentile for age and gender). Of these underweight children, fifty percent were younger than 12 months, fifty-three percent were under 6 months, and sixty-seven percent were under 2 months of age. Underweight children were significantly (p=0.01) 2.4 times (OR) more likely to be in respiratory distress (retracting) than children with normal weight.

	Proportion tachypnea n(%)	Proportion wheezing n(%)	Proportion hypoxia n(%)
<12 months n (%)	45/74 (61)	24/74 (32)	33/74 (45)
>12 months n (%)	07/09 (78)	01/09 (11)	01/09 (11)
p	0.47#	0.26#	0.07#
<6 months n (%)	41/57 (72)	17/57 (30)	28/57 (49)
>6 months n (%)	11/25 (44)	8/25 (32)	6/25 (24)
P	0.04#	1.0#	0.05#
<2 months n (%)	17/18 (94)	0/18 (0)	8/18 (44)
>2 months n (%)	35/65 (54)	25/65 (38)	26/65 (40)
p	**0.002#**	**0.001#**	**0.79#**

Table 1: Clinical manifestations of childhood CAP: Stratified by age groups.

Two-tailed Fisher's Exact test.

As shown in table 3, criteria for clinical diagnosis of pneumonia in study subjects were comparable to those in HIC [16,17]; antibiotics selection to target organisms of interest for specific age groups were comparable and appropriate [18-20]; however, vancomycin was not prescribed for late-onset pneumonia empirically as recommended in HIC. Median duration of therapy was 7 days contrasted with 10-14 days in HIC [21,22]. A Complete Blood Count (CBC) with differential was performed in only 8 of 83 (ten percent) children as opposed to recommendation in a HIC nearly all children who are hospitalized with pneumonia, particularly neonates and pneumonia complicated by hypoxia [16]. A chest radiograph was performed in only 2 percent

Tachypnea	<2months	>2 months	<6 months	>6 months
Cases	17	35	41	11
Control	1	29	16	13
Total	18	64	57	24
Odd Ratio (95% CI)	**14.08** 1.92-608.44		**3.02** 1.003-9.155	
p	0.002		0.02	
Hypoxia	<2months	>2 months	<6 months	>6 months
Cases	8	26	28	6
Control	10	39	29	19
Total	18	65	57	25
Odd Ratio (95% CI)	1.2 0.35-3.88		**3.05** 0.97-10.63	
p	0.73		0.03	
Wheezing	<2months	>2 months	<6 months	>6 months
Cases	0	25	17	8
Control	18	40	40	17
Total	18	65	57	25
Odd Ratio (95% CI)	0 *		0.90 0.296-2.904	
p	0.001		0.84	

Table 2: Risk of respiratory distress childhood CAP: Comparing age groups.

*Exact confidence levels not possible with zero count cells for <2months

Cases - with the defined conditions (tachypnea, hypoxia and wheezing)

Controls - without the defined conditions.

of neonates and 30 percent pneumonia complicated by hypoxia of the study population as opposed to recommendation in a HIC in all neonates, pneumonia complicated by hypoxia and failure to thrive.

	Study population	Standard of Care in HIC
Diagnosis	Clinical supported by pulse oximetry	Mostly clinical supported by pulse oximetry and chest radiograph
Evaluations Laboratory CBC with differential C-reactive protein Blood culture PCR*- NP^ specimen Chest radiograph	 2% neonates 26% hypoxia None None None Not routine	 Indicated in neonates; older children as necessary As above As above Suspected mycoplasma, B pertussis, & complicated viral pneumonia Not routine Indicated in all neonates and complicated pneumonia (hypoxia)
Treatment Antibiotic selection Duration of therapy	 Age -specific antibiotic appropriate Vancomycin missed - late-onset pneumonia (>3 days) 7 days (median)	 Ampicillin & Gentamicin- neonates Ceftriaxone & azithromycin->3 months Vancomycin-suspected MRSA 10 days (median) Longer In complicated cases
Follow-Up	None	Mandated in all cases

Table 3: Management of hospitalized childhood CAP cases: LMIC versus HIC.

*PCR= polymerase chain reaction ^ nasopharyngeal

A Complete Blood Count (CBC) showed a mean hemoglobin level of 9.5g/dL (range, 8.4-11.5). Findings on chest radiograph included opacities/ infiltrates (8), hyperinflation (11), cardiomegaly consistent with underlying congenital heart disease (1), and hilar lymphadenopathy (1). Pneumonia was complicated by meningitis in one patient and pulmonary tuberculosis in one patient. Hepatomegaly was detected in two patients. Antibiotics were administered to all children for a total duration of 7 days; only 4 children received antibiotics for less than 7 days (left against medical advice). Majority (53 percent) of children received antibiotics via parenteral route, forty-four percent received via parenteral route followed by oral route and four children received via oral route only. The most commonly prescribed antibiotic was ampicillin in fifty-four children followed by gentamicin in twenty-seven, ceftriaxone in sixteen and ceftazidime in only four children. Oral antibiotics included amoxicillin, cefixime, isoniazid and pyrazinamide.

Discussion

Although numerous guidelines exist regarding management of childhood pneumonia in LMIC on an out-patient basis, there is paucity of data regarding hospitalized cases. Our study is an evidence-based approach attempting to evaluate and analyze clinical management of hospitalized childhood pneumonia in a LMIC and contrast with standard of care practices in a HIC. Our data reproduce World Health Organization (WHO) data- a large number of hospitalized childhood respiratory cases in LMIC are diagnosed as bacterial pneumonia. Our numbers are also consistent with the magnitude (thirty-one percent) of childhood pneumonia as described in a recent study in Bangladesh [23]. It is very complex to establish etiology of a childhood CAP. Pneumonia is defined as infection of the lung parenchyma characterized by

an inflammatory response and fluid-filled alveoli (alveolar exudates consisting of pus and cellular debris). This finding can be manifested as a "crepitation", "crackle" or "rales" on clinical examination (auscultation) of the lungs. In HIC, diagnosis of CAP most of the time is clinical and presumptive supported by laboratory evaluation - evidence of elevated inflammatory markers in blood (commonly a CBC with differentia and a c-reactive protein) and radiological evaluation. A chest radiograph showing an evidence of consolidation is more likely a "bacterial" etiology versus a viral etiology. A definitive diagnosis can only be made when a bacterial pathogen is isolated from a sterile body fluid or site by culture or by Polymerase Chain Reaction (PCR). In severe cases, a bronchoscopy may be indicated. It is important to mention that sensitivity of a blood culture to yield a bacterial pathogen is estimated to be around 30 percent [24]. This remains one of the limitations of the study that a "presumptive" diagnosis of a bacterial cause is based only on clinical examination finding of "crepitation" or "crackles" and not supported by laboratory or radiological evaluations. Since cost is the major hurdle in this case, this remains an item for discussion and improvement in LMIC. Nevertheless, it is important to mention that viruses account for most cases of childhood CAP in both LMIC and HIC. Therefore, clinicians need to remain vigilant regarding unnecessary abuse of antibiotics in these children.

Our finding that infants under 6 months suffered higher morbidities (hypoxia) compared to their older counterparts is also consistent with data in literature [16,17,20]. Higher prevalence of wheezing in older study children can be explained by higher level of exposure of these children to environmental triggers including passive smoke, outdoor allergens, and viruses. Severity of CAP is usually assessed by chest radiography [16] in HIC and findings are found to be significantly more severe in infants (71%) compared to older children (59%) [17]. According to British Thoracic Society (BTS), pulse oximetry <92% suggests disease severity [16]. Lack of resources for radiological evaluation of pneumonia in LMIC remains a challenge. However, it is not clear what prompted radiological evaluation in some patients in our study and not in others with similar risk condition/complication-only two of the ten neonates and nine of 34 children with hypoxia had a chest radiograph performed. Thus, there was a missed opportunity to evaluate eight neonates and twenty-five hypoxia cases radio graphically. It may be reasonable to recommend pulse oximetry over a chest radiograph for assessment of these high risk pneumonia cases in LMIC for cost-effectiveness yet be productive.

It has been noted that infants and younger children who received ampicillin and gentamicin in our study were considered late-onset pneumonia/sepsis when vancomycin should have been added to cover *staphylococcus epidermidis* and Methicillin Resistant Staph Aureus (MRSA), per standard of care in HIC. This disparity could result in treatment failure in these cases. However, this management outcome could not be determined because no post-discharge follow-up of these cases was available. According to WHO, the first-line drugs recommended for hospitalized cases in LMIC are benzylpenicillin, amoxicillin and chloramphenicol, whereas ampicillin or amoxicillin plus gentamicin are recommended in the case of very severe pneumonia [18]. Other differential diagnoses to be considered include tuberculosis and malaria, in LMIC [3,25,26]. These recommendations for childhood pneumonia management in LMIC, apparently are set up to meet the main goal of treatment to reduce mortality as cheaply as possible [18-20]. A combination of a beta-lactam and macrolide antibiotic has been suggested for children aged >3 months with severe pneumonia [21,22] in HIC. This is to preclude possibility of treatment failure with macrolide monotherapy [22,27]. The usual practice in a HIC is to switch parenteral therapy to oral therapy, once clinical improvement has been demonstrated and patient can tolerate oral medication. This is to reduce healthcare costs in HIC. In the case of complications, broader spectrum antibiotics (eg., piperacillin plus a beta-lactam inhibitor or a carbapenem combined with vancomycin) are recommended. The median duration of treatment in our study was 7 days contrasted with recommended standard duration for uncomplicated cases in HIC is 10 days and longer in complicated cases as guided by the infecting pathogen isolated from a sterile body site or response to therapy.

Although it may be inferred that neonates are protected by passive immunities from their mothers up to 6 months of age, concerns with inadequate passive immunities may remain due to secondary immunodeficiency as a result of malnutrition in their mothers. Evidence exists regarding reduced placental transfer of Hib antibodies from malnourished mothers to their infants [28]. Anemia is considered a specific marker of malnutrition. Anemia was documented in all seven of our study children who tested for CBC. Although impact of anemia on disease outcome may be enormous, treatment is simple and cost-effective. A missed opportunity to evaluate for anemia in a pneumonia case may lead to serious consequences, including mortality. Additionally, a simple CBC test can offer other important relevant information related to the infection. Although, no mortality from bacterial pneumonia has been reported in our study patients, no definite statement regarding mortality can be made because no post-hospital discharge follow-up was done. This remains one of the major limitations of our study. It has been reported that most mortality in pneumonia cases occur post- hospital discharge at home in LMIC [12,13]. The outcome is even worse in the setting of an underlying malnutrition. An estimated nine percent mortality has been reported in hospitalized childhood pneumonia cases complicated by severe malnutrition post-hospital discharge in Dhaka, Bangladesh [29]. The median age of these children was 6 months, and according to the authors, were suspected to have suffered a relapse of pneumonia. The most important variables associated with post-discharge mortality were determined to be young age and malnutrition according to a multivariate analysis [30]. Severe anemia specifically has been predicted to account for higher post-hospital discharge mortality in children [15]. An estimated fifty percent of our study population may have remained at risk for post-hospital discharge mortality because fifty percent of these children were under 6 months of age and suffered malnutrition. Thus, it is strongly recommended that available resources be utilized in LMIC to augment these aspects of management in addition to treatment of infection alone with antibiotics.

While multiple interventions are needed to decrease childhood mortality from pneumonia, strategies to augment passive immunities from mothers to their infants through maternal immunization during pregnancy remain a cost-effective, wise and productive intervention to consider in LMIC. The Expanded Program for Immunization schedule for children administers Hib and SPN as routine standard of care starting at 6 weeks of age. Concerns remain for emergence of non-vaccine serotypes following vaccination with conjugate vaccines [31-35]; additionally, the available conjugate vaccines contain serotypes which are not compatible for prevalent serotypes in LMIC. Thus, maternal immunization with 23-valent polysaccharide SPN and Hib vaccines during pregnancy may be one of the most cost-effective strategies to protect infants against these bacteria during this vulnerable period of their lives.

Development and implementation of a structured program for objective assessment of severity of childhood pneumonia supported by minimal laboratory, pulse oximetry and imaging procedures is critical for adequate management of hospitalized childhood pneumonia cases in LMIC. This program development can also take into account assessment of metabolic biomarkers addressing nutritional status of patients (total protein and albumin levels) at a minimum. An elaborate discharge planning with a definite follow up care plan is warranted. Role of a social worker is well recognized in discharge planning and follow up care of socially disadvantaged population. Thus, distribution of resources should be made wisely in a cost-effective manner and for the most productive outcome. This opportunity should also be sought to update vaccination status of children and caregivers' education regarding disease prevention (e.g., avoidance of passive smoke exposure and exclusive breast feeding) prior to hospital discharge. Extended program development may need to be set up to identify and address barriers to follow-up care post-hospital discharge including transport, caregivers' loss of wages, and caregivers' education and awareness as well.

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