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Diagnostic and Prognostic Roles of C-Reactive Protein in Childhood Pneumonia

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Abstract

A hospital-based, case-control study was conducted in the Department of Pediatrics in Community Based Medical College, Bangladesh (CBMC,B) Hospital, Mymensingh, Bangladesh, between February and September of 2013, to determine the role of CRP for the diagnosis of pneumonia as well as treatment response of pneumonia. A total of 180 children with pneumonia were enrolled – 90 as case (group A) and another 90 having ARI other than pneumonia as control (group B), based on specific inclusion and exclusion criteria. Necessary information was collected by detailed history taking, clinical examination and close follow-up in the hospital, by using a pre-designed data sheet. The mean±SD age of the participants as case (group A) and control (group B) were 8.53±10.24 and 6.68±3.59 respectively (P>0.05). Male children were 66(73.3%) and 68(75.6%), while female children were 24(26.7%) and 22(24.4%) in group A and group B respectively (P>0.05). In two groups, the mean CRP before treatment were 48.80±32.4 and 3.60±1.30 respectively; the difference was statistically significant (P<0.001), which signifies that those who were suffering from pneumonia had an initial CRP response much higher than those who were suffering from other forms of respiratory diseases. Among antibiotic responders, symptoms and signs resolved in approximately 2-4 days; however, among non-responders, symptoms even persisted >7 days. Among the responders, CRP was significantly reduced after treatment (P<0.001); in contrast, among non-responders, even after treatment, no or little reduction in CRP was observed (P>0.05). Hence, we suggest that measuring CRP to see the antibiotic response in childhood pneumonia is helpful.

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Introduction

Pneumonia remains leading cause of death in children under five years in low- and middle-income countries despite the introduction of case management guidelines and the development of new preventive strategies including effective vaccines.[1] Pneumonia currently accounts for 18 percent of annual death in under five children worldwide, 20% in low-income countries compared to only 4.3% in high income countries.[1] Annually, 150 million new episodes occur worldwide.[2] 74 percent of new episode occur in just 15 countries, more than half in just 6 countries: India, China, Pakistan, Bangladesh, Indonesia and Nigeria.[3] Bangladesh has the 5th highest rate of pneumonia in the world, with an estimated 6 million cases, and 50,000 deaths annually among children under 5 years.[4] Population-based studies have reported a high incidence of pneumonia among children aged <5 years who live in rural areas (0.23 episodes per child-year) and urban areas (0.56 episodes per child-year) in Bangladesh.[5]

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Bacteria and viruses are mostly etiological agents of pneumonia. Among the bacterial etiology, *Streptococcus pneumoniae* and *H. influenzae* are the main cause of childhood pneumonia.[6] Viral causes were found in 45% of hospitalized children.[7] Isolation of organisms is the gold standard in diagnosis of pneumonia. However, availability of blood culture and sensitivity in childhood pneumonia is only 10% in rural and remote areas,[7,8] which is especially true for a country like Bangladesh. In Bangladesh, a study showed that consolidation was found in the chest radiograph only in 52% of childhood pneumonia.[8]

Although leucocytosis is one of the common features of bacterial pneumonia, research showed that 21% of pneumococcal pneumonia may reveal a normal leucocyte count.[9] CRP is a better indicator of radiographic diagnosed cases of bacterial pneumonia than absolute neutrophil count or white blood cell count.[10] Since assessment of the specific microbial etiology of pneumonia is difficult, nonspecific inflammatory biomarkers are widely used for this purpose.[11]

A commonly used biomarker is CRP. Determination of the serum concentration of CRP is a rapid, simple, and inexpensive procedure.[12] CRP is superior to ESR in terms of rapidity of response and specificity of inflammation.[13] It is a more precise, reproducible, and quicker performed test than the erythrocyte sedimentation rate (ESR).[12] CRP is an independent marker of severity in community acquired pneumonia.[14] CRP level of 40 mg/dl or greater, with a clinical diagnosis of pneumonia, identifies a greater proportion of pneumococcal pneumonias than does clinical diagnosis alone.[15]

The Quick Read-CRP test to be a useful predictor of bacterial pneumonia in children, especially those with a shorter duration of illness.[13] CRP is not only used to diagnose pneumonia, but also to monitor the patient's response to therapy.[12] Consecutive CRP measurements have become routine clinical practice in the follow up of patients admitted in hospital with severe infection.[11] Delayed normalization of CRP level increased risk of inappropriate treatment or treatment failure in patients of pneumonia.[16,17] A decline of >60% CRP level in 1st 3 days and >90% CRP level in 7 days in a patient of pneumonia indicate the appropriate initial treatment was given or appropriateness of empirical treatment.[17] To our knowledge, only few studies were conducted in Bangladesh about diagnostic value of CRP in pneumonia and uses of CRP in the follow up of treatment of pneumonia. In this point of view this study will be conducted to know the diagnostic and prognostic value of CRP in pneumonia among children age between 2 months to 5 years in Bangladesh and the result of this study may help in better management of pneumonia.

Methods

This hospital based, case-control study was conducted in the Department of Pediatrics in Community Based Medical College, Bangladesh (CBMC,B) Hospital, Mymensingh, Bangladesh, between February and September of 2013. A total of 180 children with Acute Respiratory Infection (ARI) were enrolled – 90 having pneumonia as case (group A) and another 90 having ARI other than pneumonia as control (group B), based on specific inclusion and exclusion criteria. Inclusion criteria for the case (group A) included: aged between 2 months and 5 years, cough, fever, respiratory distress (fast breathing and or chest indrawing) and patchy opacity or consolidation in the chest radiograph.

For control (group B), the inclusion criteria were: aged between 2 months and 5 years, cough, fever, respiratory distress (fast breathing and or chest indrawing) and no patchy opacity or consolidation found in the chest radiograph. Exclusion criteria included: congenital heart diseases, children required ICU management and children received treatment by antibiotic or steroid within the last 48 hours.

After proper counseling a written informed consent was taken from the guardian of the patient. Physical examination was done meticulously after taking a detailed history from mother or any other caregiver. Digital chest x-ray was done. Those who had patchy opacity or consolidation were enrolled as cases and those whose x-ray did not show patchy opacity or consolidation were enrolled as controls. Blood sample (2-3ml venous blood) were collected from both case and control with all aseptic precaution before started treatment. Then serum CRP levels were measured by using agglutination method. For cases appropriate treatment was given and proper follow up was done of main outcome variables for 7 days. Initial treatment started with Inj. ceftriaxone plus Inj. flucloxacillin (50-100 mg/kg) only for cases. For control, appropriate treatment was given according to hospital protocol. After 7 days of follow up, blood samples were collected to see the serum CRP levels. All necessary information was recorded in predesigned structured cases record form. All precautions were taken to protect the anonymity of the participating subjects.

All data were checked, rechecked, and scrutinized by two of the investigators following standard procedure. Data were analyzed by using SPSS (Statistical Package for the Social Sciences) version 16.0 for Windows. Categorical variables were reported as frequency and percentage, while numerical variables were expressed as mean±SD. Correlation was carried out using Student's 't' test (Paired and unpaired), Chi-square (X^2) test through determining the association of different variables. For all analytical tests, the level of significance was set at 0.05 and P<0.05 was considered significant. The study was approved by the Ethical Review Committee of Community Based Medical College, Bangladesh (CBMC,B), Mymensingh, Bangladesh.

Results

Age distribution in both groups were: 2-5 months 40(44.4%) and 44(48.9%), 6-10 months 26(28.9%) and 32(35.6%), 11-15 months 15(16.7%) and 12(13.3%),16-20 months 3(3.3%) and 2(2.2%) and >20 months 6 (6.7%) and 0(0.0%) respectively. The mean±SD age of the participants as case (group A) and control (group B) were 8.53±10.24 and 6.68±3.59 respectively; however, the difference was not statistically significant (P>0.05) (Table-I).

Table-I: Age distribution of the children (n=180)

Age group (months)	Group A (Case) (n=90)	Group B (Control) (n=90)	P value
1-5	40(44.4%)	44(48.9%)	0.11^{ns}
6-10	26(28.9%)	32(35.6%)	
11-15	15(16.7%)	12(13.3%)	
16-20	3(3.3%)	2(2.2%)	
> 20	6(6.7%)	-	
Total	90(100%)	90(100%)	
Mean±SD (months)	8.53±10.24	6.68±3.59	

Data were expressed as frequency and percentage. P reached from independent student t-test; ns=Not significant.

Male children were 66(73.3%) and 68(75.6%) in case and control groups, while female children were 24(26.7%) and 22(24.4%) respectively; the difference was not statistically significant (P>0.05) (Table-II).

Table-II: Distribution of children by sex (n=180)

Sex	Group A (Case) (n=90)	Group B (Control) (n=90)	P value
Male	66(73.3%)	68(75.6%)	0.73^{ns}
Female	24(26.7%)	22(24.4%)	
Total	90(100.0%)	90(100.0%)	

Data were expressed as frequency and percentage. P value reached through Chi-square test; ns=Not significant.

Symptoms and signs in group A patients were: runny nose 8(8.9%), sneezing 2(2.2%), cough 90(100%), fever 90(100%), respiratory distress 90(100%), feeding difficulty 68(75.6%), rhonchi 46(53.5%), crepitation 74(86%), severe malnutrition 22(24.4%), moderate malnutrition 21(23.3%) and mild malnutrition 47(52.2%). Symptoms and signs in group B patients were: runny nose 44(48%), sneezing 1(1.1%), cough 90(100%), fever 90(100%), respiratory distress 90(100%), feeding difficulty 36(40%), rhonchi 72(80%), crepitation 31(34%), mild malnutrition 68(75.6%), moderate malnutrition 15(16.7%) and severe malnutrition 7(7.78%) (Table-III). Mean CRP in group A was 48.80±32.4 and in group B was 3.60±1.30. The difference between cases and control was statistically significant (P<0.001) (Table-IV). Those who were suffering from pneumonia had an initial CRP response much higher than those who were suffering from other forms of respiratory diseases. Table-V shows that among antibiotic responders, symptoms and signs resolved in approximately 2-4 days; however, among non-responders, symptoms even persisted >7 days. Clinically improved patient after treatment their initial mean CRP was 50.51±30.82 and after treatment 7.53±2.64. Those who are clinically improved their CRP also significantly reduced (P<0.001). Patients those who are non-responder, that means clinically not improved their initial CRP was 72±27.71 and after treatment CRP was 60±24.1 Those who are clinically not improved their CRP also not significantly reduced (P>0.05) (Table-VI).

Table-III: Distribution of symptoms and signs of pneumonia (n=90)

Symptoms	Group A (Case)	Group B (Control)
Runny nose	8(8.9%)	44(48%)
Sneezing	2(2.2%)	1(1.1%)
Cough	90(100%)	90(100%)
Fever	90(100%)	90(100%)
Difficulty in respiration	90(100%)	90(100%)
Feeding difficulty	68(75.6%)	36(40%)
Rhonchi	46(53.5%)	72(80%)
Crepitation	74(86%)	31(34%)
Malnutrition		
Mild	47(52.2%)	68(75.6%)
Moderate	21(23.3%)	15(16.7%)
Severe	22(24.4%)	7(7.78%)

Data were expressed as frequency and percentage.

Table-IV: Comparison of CRP between two study groups (n=180)

CRP	Group A (Case) (n=90) Mean±SD	Group B (Control) (n=90) Mean±SD	P value
Before treatment	48.80±32.4	3.60±1.30	<0.001^{s}

P value reached from independent student t-test; s = Significant.

Table-V: Mean duration of treatment response (by resolving symptoms and signs) (n=90)

Variables	Treatment responder (in days) (n=86)	Treatment non-responder (in days) (n=4)
Cough	4	>7
Fever	2	>7
Respiratory rate	3	5
Chest indrawing	2	>7
Return of ability to feed	2	5

Table-VI: Prognostic value of CRP (by responding to treatment)

CRP	Before treatment Mean±SD	After treatment Mean±SD	P value
Responder (n=86)	50.51±30.82	7.53±2.64	<0.001^{s}
Non responder (n=4)	72±27.71	60±24.1	>0.05^{ns}

P value reached from independent student t-test; s=significant, ns=not significant.

Discussion

Pneumonia remains leading cause of death in children under five years in low- and middle-income countries despite availability of case management guidelines and development of preventive strategies including effective vaccines.[1] Isolation of organisms is the gold stander for the diagnosis of pneumonia. Although leucocytosis is a common feature of bacterial pneumonia, Furer *et al.* showed 21% of bacteraemic pneumococcal pneumonia there is a normal leucocyte count at presentation.[9] CRP is a better indicator of radiographic diagnosed cases of bacterial pneumonia than absolute neutrophil count or white blood cell count.[13]

In our study, 90 cases with pneumonia and 90 control with respiratory tract infection other than pneumonia were included. Male-female ratio was approximately 1.1:1 both in case and control groups. This nearly approaches other studies.[18,19] Age distribution of our study also matched with some other previous studies.[18,19]

In the present study, 90 cases enrolled in Group A. Mean CRP in case group (before starting any treatment) 48.80±32.4, while in control group was 3.60±1.30 (P<0.001). Those who were suffering from pneumonia, their initial CRP responses were very much higher than those suffering from other than pneumonia. Korppi[19] reported that those children who were suffering from bacterial pneumonia, their CRP concentrations were 30-60 mg/dl. The study reported a positive predictive value of 64%. Other than pneumonia cases, CRP level was 2.5 times less than that of pneumonia cases. Other studies reported that the sensitivity and positive predictive value of CRP level greater than 35 mg/l for diagnosis of pneumonia was 100%.[17,18,20] Our study showed similar results.

In the present study, 90 patients in case group were treated with appropriate antibiotics. Among them, 86 patients responded clinically. Mean duration of normalization of their cough, fever, respiratory rate, chest indrawing and return of feeding ability 4 days, 2 days, 3 days, 2 days, and 2 days respectively. 4 patients did not respond to treatment and their signs and symptoms persisted for more than 7 days. Among the responder (n=86), mean CRP before treatment was 50.51±30.82 mg/l and after

treatment 7.53±2.64 mg/l. Comparison of CRP of responder before and after treatment is significant P<0.001). Among the non responder (n=4)), mean CRP before treatment was 72±27.71 mg/l and after treatment 60±24.1 mg/l. Comparison of CRP of non responder before and after treatment was not significant (P>0.05). This finding was consistent with many previous studies.[11,12,14,16-20] Babu *et al.*[20] also reported through serial monitoring of CRP level during treatment that fall in CRP concentration provided the earliest clue to therapeutic response before other clinical signs like fall in temperature or respiratory rate and ESR.

Conclusion

From the results of our study, we may conclude that CRP level before treatment by antibiotic is a useful index for diagnosis of childhood pneumonia. It is also a useful index to see the treatment response in pneumonia in hospital setting as well as community level. We may recommend that in all cases of clinical pneumonia, it is necessary to perform CRP level to diagnose and to see the treatment response. However, a large-scale study through multicentre trial with larger sample size is also recommended for further evaluation.

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