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A hospital based analytical observational study to assess CRP levels in children with acute bronchiolitis

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Abstract
Aim: This study was aimed at assessing the frequency of elevated CRP in children with acute bronchiolitis and at comparing the clinical characteristics, laboratory and radiological findings, antibiotics use, and outcome according to CRP levels.
Methods: This was a retrospective, cross-sectional, and analytical study where the medical records of all patients with a clinical impression of acute bronchiolitis who were admitted to the pediatric department for the period of one year were retrieved. During the study period, a total of 200 patients were admitted with a clinical presentation of acute bronchiolitis. 50 (25%) patients were excluded due to of unavailability of data of CRP levels. The remaining 150 (75%) patients were included in the study.
Results: 85 (53.34%) patients were males. The most common clinical presentation was cough (120 (80%) patients) followed by fever (105 (70%) patients). Antibiotics were used in 80% patients. 6% patients required intensive care, 2% had surgical intervention, 2% required endotracheal intubation, and 1 (1%) died. Patients with high CRP were older at presentation (p<0:0001) and had more fever (p<0:0001) and cough (P = 0:002), but lower hemoglobin level (p<0:0001) compared to those with normal CRP. Fever (P = 0:016) and hemoglobin level (P = 0:002) were independent factors.
Conclusion: Most children with acute bronchiolitis had high rate of elevated CRP values that did not correlate with the rate of bacterial coinfection. High CRP levels were found in older children, those presented with more fever and cough, and had a lower hemoglobin level despite that those factors were previously reported to be associated with disease severity and bacterial coinfection.

Keywords: CRP, bronchiolitis, antibiotics, children

Introduction
C-reactive protein is an acute phase protein synthesized by the liver in response to a number of stimuli involving tissue damage. Interleukin-6 (IL-6) and other cytokines such as tumour necrosis factor (TNF), IL-I and transforming growth factor are also involved in CRP production [1, 2]. A number of conditions stimulate CRP synthesis including pulmonary infarction, inflammation, and neoplasia though bacterial infections are most potent stimuli leading to marked elevation in serum CRP levels within a few hours. Pneumonia elicits a powerful inflammatory response, both locally and systemically with chemotatic cytokine release into the peripheral circulation. There have only been scanty reports of the diagnostic utility of CRP in pneumonia. CRP has also been shown to be helpful in distinguishing bacterial and viral pneumonia [3].
CRP has also been used as an index of response to treatment in rheumatic fever and certain other conditions. CRP is tested either by capillary precipitation of patients sera with antisera prepared in rabbits against purified CRP or by passive agglutination using latex particles coated with anti CRP antibody [4]. Antimicrobial resistance is a growing threat and will not only result in unnecessary exposure to side effects and increased healthcare costs, but also increased morbidity and mortality [5, 6]. A recent study estimated 1.27 millions deaths attributable to antimicrobial resistance in 2019 [7].
Acute bronchiolitis, a lower respiratory tract infection very common in children, is a viral infection with respiratory syncytial virus (RSV) the agent most frequently implicated [8, 9]. Other agents, such as the parainfluenza virus and some adenoviruses may be found, however [9]. It is characterised by acute inflammation, oedema, and necrosis of epithelial cells

lining small airways, with consequent obstruction. It is manifested clinically by cough, tachypnea, the use of accessory respiratory muscles, wheezing and crackles heard on lung auscultation [8]. In addition, raised CRP levels are more frequently found in patients with respiratory tract infection caused by adenovirus that those with an RSV or influenza infection6. Several studies have tried to establish the use of CRP levels in distinguishing lower respiratory tract, viral and bacterial infections. They show that the high CRP levels are likely to have a bacterial cause [10, 1], but the remaining cases have very similar inter-group results, making it hard to distinguish a viral from a bacterial pneumonia based on CRP measurements PCR [11].

This study was aimed at assessing the frequency of elevated CRP in children with acute bronchiolitis and at comparing the clinical characteristics, laboratory and radiological findings, antibiotics use, and outcome according to CRP levels.

Materials and Methods

This was a retrospective, cross-sectional, and analytical study where the electronic medical records of all patients with a clinical impression of acute bronchiolitis and were admitted to the pediatric department for the period of one year were retrieved. During the study period, a total of 200 patients were admitted with a clinical presentation of acute bronchiolitis. 50 (25%) patients were excluded due to of unavailability of data of CRP levels. The remaining 150 (75%) patients were included in the study.

Children below the age of five years who were admitted with acute bronchiolitis, had a nasopharyngeal swab for RSV infection tested via direct antigen detection and/or polymerase chain reaction (PCR), and CRP level checked were included in this study. Patients were suspected to have acute bronchiolitis based on the criteria published by the American Academy of Pediatrics. The criteria indicate that the diagnosis is based on signs and symptoms suggesting bronchiolitis including rhinorrhea, cough, tachypnea, wheezing, rales, and increased respiratory effort manifested as grunting, nasal flaring, and intercostal and/or subcostal retractions. Radiographic or laboratory investigations should not be routinely used to diagnose acute bronchiolitis.[13] CRP levels were tested using enzyme-linked immunosorbent assay (ELISA) technique and presented as quantitative figures. Normal CRP value was ≤3mg/L.

Data Collection

Demographic data including sex, gestational age, age at presentation, clinical presentation, length of stay, and age at the time of study were collected. Results of laboratory investigations including complete blood count, CRP levels, blood culture, urine culture, and cerebrospinal fluid (CSF) culture, and nasopharyngeal swab for RSV direct antigen detection and/or PCR were retrieved. Results of respiratory viral serology profile test (immunoglobulin M and G) for legionella pneumophilia, mycoplasma pneumonia, coxiella burnettii, chlamydia pneumonia, adenovirus, RSV, influenza A and B, and parainfluenza were gathered. Radiological findings on the chest X-ray reported by senior radiologists were documented. Medical therapy including antibiotic use, patient's outcome, and complications were also evaluated.

Ethical Approval

This study was conducted in accordance with the Helsinki declaration and was ethically approved by the Research and Research Ethics Committee.

Statistical Analysis

The data were statistically analyzed using SPSS version 21 software. Demographic data were presented as frequencies and percentages. Normally distributed continuous variables were presented as mean and standard deviation (SD). Median and interquartile range (IQR) were calculated for nonnormally distributed variables. Chi-Square Fisher's test was used to compare categorical variables. Student's T-test or Mann–Whitney U-test was used to compare continuous variables. Variables found to be significant in the univariate analysis and had no multicollinearity using a variation inflation factor > 8 were included in a binary logistic regression to detect the independent factors of high CRP levels. P value < 0.05 was considered statistically significant. Confidence interval was set at 95%.

Results

Table 1: Demographic data of children with acute bronchiolitis

Demographic data	N	%
Gender		
Male	80	53.34
Female	70	46.66
Age at presentation (mon), median (IQR)		3.5 (1.27-12.33)
Current age (y), median (IQR)		1.35 (1.14-2.1)
Length of stay (d), median (IQR)		5.0 (3.0-8.0)
Clinical symptoms		
Cough		120 (80)
Fever		105 (70)
Rhinorrhea		105 (6.66)
Shortness of breathe		50 (33.34)
Reduced feeding		45 (30)
Vomiting		36 (24)
Hypoactivity		24 (15)
Sepsis		12 (8)
Cyanosis/Desaturation		12 (8)
Nasal blockage/Congestion		12 (8)
Diarrhoea		12 (8)

85 (53.34%) patients were males. The most common clinical presentation was cough (120 (80%) patients) followed by fever (105 (70%) patients).

Table 2: Blood investigations for 150 children with acute bronchiolitis

Investigation	Mean	SD	Median	Minimum	Maximum	Normal range
White blood cells count (×106/µL)	11.4	8.6	9.6	0.8	111.4	3.6-9.6
Hemoglobin (g/dL)	11.3	2.2	10.9	5.7	20.0	12-14.5
Platelet's count (×106/µL)	418.5	176.4	393.0	14.5	971.0	150-400
C-reactive protein (mg/L)	27.5	39.0	10.4	0.1	297.0	0-3

Table 3: Comparison between C-reactive protein positive and negative patients

Variable		C-reactive protein level		P Value
		High n=100	Low n=50	
Gender	Male	60 (60)	27 (54)	0.450
	Female	40 (40)	23 (46)	
Age at presentation (mon), mean ± SD		11:76 ± 13:91	6:26 ± 17:60	<0.0001
Age at the time of study (mon), mean ± SD		32:22 ± 14:20	27:07 ± 17:44	<0.0001
Length of hospital stay (d), mean ± SD		10 ± 39	12 ± 69	0.250
History of fever		82 (82)	26 (52)	<0.0001
History of cough		81 (81)	31 (62)	0.002
White blood cells count (×106/μL), mean ± SD		11:92 ± 9:65	9:95 ± 4:78	0.131
Hemoglobin (g/dL), mean ± SD		10:9 ± 1:8	12:5 ± 2:7	<0.0001
Platelet's count (×106/μL), mean ± SD		417:3 ± 175:5	421:6 ± 180:1	0.910
Positive blood culture		10 (10)	4 (8)	0.780
Positive urine culture		10 (10)	4 (8)	1.000
Positive cerebrospinal fluid culture		4 (4)	0	1.000
Positive chest X ray		70 (70)	32 (64)	0.630
Antibiotic use		80 (80)	35 (70)	0.064
Complications		10 (10)	5 (10)	1.000
Admission to intensive care unit		6 (6)	3 (6)	0.750
Mortality		1 (1)	2 (0.5)	1.000

Antibiotics were used in 80% patients. 6% patients required intensive care, 2% had surgical intervention, 2% required endotracheal intubation, and 1 (1%) died. Patients with high CRP were older at presentation (p<0:0001) and had more fever (p<0:0001) and cough (P = 0:002), but lower hemoglobin level (p<0:0001) compared to those with normal CRP. Fever (P = 0:016) and hemoglobin level (P = 0:002) were independent factors.

Discussion

In primary care, infectious disease in children is very common. Most common are non-serious, self-limiting infections. Less than 1% will have a serious infection [12]. However, serious infections can be associated with both significant morbidity and mortality [12, 13]. Therefore, recognition remains crucial. Nevertheless, differentiating serious from non-serious infections can be difficult. C-reactive protein (CRP), which is an acute phase reactant and one of the indicators of acute inflammation, has been linked to bacterial coinfections like bacterial pneumonia [14, 15]. However, it was shown that patients with RSV bronchiolitis, bronchopneumonia, and RSV pneumonia had elevated levels of CRP along with higher white blood cells (WBC) count and erythrocyte sedimentation rate (ESR) which all indicate bacterial coinfection [14-16]. Accordingly, identification of CRP levels can be an important indirect marker for viral infections and an indicator for progression of infection and effectiveness of the treatment.[14] In patients with RSV bronchiolitis, it is worth mentioning that elevated CRP levels were associated with prolonged length of hospital stay [14, 17, 18].

RSV infection predominance in males is well-known but its mechanism has not been explored up till now. This finding might be attributed to the suppression of blood eosinophil cell count or due to the immunosuppressive effect of male hormones. In our study, male patients had higher CRP levels compared to females. Yet, sex was not a significant risk factor for high CRP. Conversely, Nagayama *et al*. showed that higher CRP levels were found to be more in females (37.8%) compared to males (19%) p<0:05. This variation has been also explained by the presence of immunologic differences between boys and girls [19].

The most common clinical presentations of patients with acute bronchiolitis in this study were cough (80%) and fever (70%), which is ingoing with the findings of several other studies [20-22]. Nonetheless, cough was more frequent in Lamarão *et al*. and Sawatzky *et al*. studies (97.9% and 93.3%, respectively); but the fever was of less frequency (72.4% and 51.7%, respectively) [20, 22]. For the laboratory investigations, the current study had a median WBC count of 9.6 g/dL, which was similar to what was reported by Do *et al*. (9.7 g/dL) [21]. Mean WBC count in our study was higher in children with high CRP compared to those with normal levels, but this was not statistically significant. Similarly, Fares *et al*. found that WBC count was not predictive for bacterial coinfection in children with bronchiolitis [18]. Nonetheless, majority of children with viral infections have low WBC counts [16]. Moreover, WBC count did not differ between RSV-positive and RSV-negative infants in Resch *et al*.'s study [23].

Despite that there was no significant difference between RSV-positive and RSV-negative patients in terms of the percentage of patients with high CRP levels, the mean CRP level was found to be significantly lower in RSV positive (21:5 ± 27:7mg/L) compared to RSV-negative patients (31:3 ± 44:3 mg/L) in this study (P = 0:042). Peltola *et al*.'s study showed that most children with viral infections has low CRP levels including those with RSV [16]. This finding might be attributed to the presence of a higher percentage of bacterial coinfections in the RSV-negative patients which might not be detected by blood, urine, or CSF cultures. However, Resch *et al*. found that CRP levels did not differ between RSV-positive and RSV-negative infants [23].

Patients with acute severe bronchiolitis who needed to be admitted to the PICU are usually sicker, may require mechanical ventilation, or have an associated bacterial coinfection. In contrary, those managed in general pediatric wards usually have a milder disease. Seriously ill infants with extensive consolidation or atelectasis had significantly higher CRP levels in Papoff *et al*.'s study (P = 0:04) [24]. Moreover, CRP values had a statistically significant relation with PICU admissions (P = 0:008) in Tavares M *et al* study which hypothesized that CRP levels might serve as indirect markers of disease severity [25]. Accordingly, patients admitted to the PICU tend to have higher CRP levels

compared to those not. Despite that the mean CRP levels in the present study were higher in patients admitted to the PICU compared to those not, this difference was not statistically significant. This study also showed no significant differences between patients with high CRP levels and those with normal levels in terms of complications and mortality rate. Similar to our study, Fares *et al*. [16] and Resch *et al*.'s studies showed that acute bronchiolitis severity was not influenced by the CRP levels [23].

Conclusion

This study showed that most patients with acute bronchiolitis had high rate of elevated CRP values that did not correlate with the rate of bacterial coinfection. Children with high CRP levels were older at presentation, presented with more fever and cough, and had a lower hemoglobin level despite that those factors were previously reported to be associated with the disease severity and bacterial coinfection. This study also showed a high overall rate of antibiotic prescriptions in a mostly viral disease. Further studies to figure the critical CRP cut-off that might be of highly suspicious for bacterial infection and to build a clinical management algorithm to minimize the unnecessary use of antibiotics in children with acute bronchiolitis are needed.

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