Journal of Chemical Health Risks

www.jchr.org

JCHR (2022) 12(4), 737-741 | ISSN: 2251-6727

A Retrospective Assessment of CRP Levels in Children with Acute Bronchiolitis: An Observational Study

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KEYWORDS

C-reactive protein, acute bronchiolitis, children

ABSTRACT:

Aim: The aim of the present study was to assess the frequency of elevated CRP in children with acute bronchiolitis.

Material & methods: A retrospective assessment of children with acute bronchiolitis admitted to Department of Pediatrics, GS Medical College, Pilkhuwa, Uttar Pradesh. Demographic, clinical, laboratory and radiological data, and outcomes were collected. Patients with high CRP were compared with those with normal levels for the duration of 12 months. Total 200 patients were included in the study.

Results: Of 200 patients, 120 (60%) were males. Median presentation age was 3.9 (interquartile range (IQR), 1.27-12.33) months. The most common clinical presentation was cough (160 (80%) patients) followed by fever (152 (76%) patients). Median CRP level was 10.5 (IQR, 2.8-35.1) mg/L. CRP was high in 150 (75%) patients. Respiratory syncytial virus (RSV) was detected in 70 patients. 170/200 patients had positive chest X-ray. Antibiotics were used in 140/20 patients. The significant variables were tested for multicollinearity (VIF > 8) between each other and were put into a logistic regression model. Accordingly, fever (P = 0.018) and hemoglobin level (P = 0.003) were found to be the independent predictor for high CRP levels.

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.

1. INTRODUCTION

Acute bronchiolitis is one of the most common respiratory diseases in children younger than two years of age.[1] It is more common in preterm newborns and in male patients. [2,3] It is a lower respiratory tract infection that affects approximately 20% of all children, resulting in hospitalization for 2-3% of them under 12 months of age. Mortality from AB occurs predominantly in developing countries. In developed countries it is associated with various complex chronic conditions and sociodemographic risk factors.[4] Acute bronchiolitis-related morbidity and mortality are much higher in premature infants and in infants with chronic lung disease or congenital heart diseases. [5] AB classically presents with increased respiratory effort and wheezing, often accompanied by systemic manifestations such as fever or apnea, a common symptom in neonates. a common disease is of 14-21 days with peak symptoms at days 3-5. The most common viral pathogen associated with bronchiolitis is Respiratory Syncytial Virus (RSV), which accounts for 50-80% of cases, and is associated with more severe disease.[4] Pneumonia elicits a powerful inflammatory response, both locally and systemically with chemotatic cytokine release into the peripheral circulation.

C-reactive protein is an acute phase protein synthesised 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. [6,7] Peaking 48-72 hours after the onset of an inflammatory response, it is a common clinical tool for diagnosis and monitoring of inflammatory responses.[4] It is one of the indicators of acute inflammation, has been linked to bacterial coinfections like bacterial pneumonia.[8,9]

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. [8,9,10]

Journal of Chemical Health Risks
www.jchr.org
JCHR (2022) 12(4), 737-741 | ISSN: 2251-6727

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.[8] In patients with RSV bronchiolitis, it is worth mentioning that elevated CRP levels were associated with prolonged length of hospital stay.[1,8,11] Data about the association between acute bronchiolitis and CRP levels are scares.

Hence the aim of the study was to assessing the frequency of elevated C-reactive protein (CRP) levels in hospitalized children presented with acute bronchiolitis.

2. MATERIAL & METHODS

A retrospective reviewed medical record of children with acute bronchiolitis admitted to Department of Pediatrics, GS Medical College, Pilkhuwa, Uttar Pradesh. Demographic, clinical, laboratory and radiological data, and outcomes were collected. Patients with high CRP were compared with those with normal levels for the duration of 12 months. Total 200 patients were included in the study.

Inclusion criteria

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. [12]

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.[12] Radiographic or laboratory investigations should not be routinely used to diagnose acute bronchiolitis. [12] CRP levels were tested using enzyme-linked immunosorbent assay (ELISA) technique and presented as quantitative figures. Normal CRP value was ≤3mg/L. This study was conducted in accordance with the Helsinki declaration and was ethically approved by the Research and Research Ethics Committee for Government hospitals, Salmaniya Medical Complex, Bahrain. Signed informed consent was taken from each child's parent or legal guardian upon admission.

METHODOLOGY

Demographic data including sex, nationality, 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.

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). P value < 0.05 was considered statistically significant. Confidence interval was set at 95%.

3. RESULTS

Table 1: Demographic data

Gender	**N%**
Male	120 (60)
Female	80 (40)
Age at presentation (mon), median (IQR)	3.9 (1.27-12.33)
Current age (y), median (IQR)	1.40 (1.14-2.1)
Length of stay (d), median (IQR)	4.0 (3.0-8.0)

Of 200 patients, 120 (60%) were males. Median presentation age was 3.9 (interquartile range (IQR), 1.27-12.33) months.

Table 2: Clinical presentations

Clinical presentations	**N%**
Cough	160 (80)
Fever	152 (76)
Rhinorrhoea	56 (28)
Shortness of breathing	46 (23)

Journal of Chemical Health Risks
www.jchr.org
JCHR (2022) 12(4), 737-741 | ISSN: 2251-6727

Reduced feeding	40 (20)
Vomiting	38 (19)
Hypoactivity	28 (14)
Sepsis	8 (4)
Cyanosis/Desaturation	8 (4)
Nasal congestion/Blockage	8 (4)
Diarrhoea	8 (4)

The most common clinical presentation was cough (160 (80%) patients) followed by fever (152 (76%) patients).

Table 3: Blood investigations

Investigation	Mean	SD	Median	Minimum	Maximum	Normal range
White blood cells count ($\times 10^6/\mu$L)	12.5	8.8	9.6	0.9	112.4	3.6-9.6
Hemoglobin (g/dL)	11.6	2.4	11.9	5.8	21.0	12-14.5
Platelet's count ($\times 10^6/\mu$L)	420.6	176.5	396.0	14.6	972.0	150-400
C-reactive protein (mg/L)	28.4	38.0	10.5	0.2	298.0	0-3

Median CRP level was 10.5 (IQR, 2.8-35.1) mg/L.

Table 4: Comparison between C-reactive protein positive and negative patients

Variable		High, 150 (75)	Normal, 50 (25)	P Value
Sex	Male	90	26	0.414
	Female	60	24	
Gestational age	Term	120	40	1.000
	Preterm	30	10	
Age at presentation (mon), mean ± SD		12:78 ± 14:86	7:23 ± 16:64	<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		11 ± 38	13 ± 69	0.216
History of fever		115	26	<0.0001
History of cough		110	32	0.002
White blood cells count ($\times 10^6/\mu$L), mean ± SD		12.82 ± 8.64	9.81 ± 4.66	0.136
Hemoglobin (g/dL), mean ± SD		10.5± 1.6	12.6± 2.7	<0.0001
Platelet's count ($\times 10^6/\mu$L), mean ± SD		418.2 ± 174.6	421:6 ± 180:1	0.910
Positive blood culture (*n=100)*		10	4	0.775
Positive urine culture (*n* = 90)		9	3	1.000
Positive cerebrospinal fluid culture (*n* = 20)		1	0	1.000
Positive chest X ray (*n* = 170)		130	40	0.624
Positive RSV test (*n* = 175)		70	20	0.364
Antibiotic use (*n* = 180)		140	40	0.060
Complications		2-	8	1.000
Admission to intensive care unit (*n* = 180)		5	3	0.740
Mortality (*n* = 180)		2	1	1.000

CRP was high in 150 (75%) patients. Respiratory syncytial virus (RSV) was detected in 70 patients. 170/200 patients had positive chest X-ray. Antibiotics were used in 140/20 patients.

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JCHR (2022) 12(4), 737-741 | ISSN: 2251-6727

Table 5: Binary logistic regression analysis

Variables	Adjusted odd ratio	95% Cl	P Value
Age at presentation (m)	0.886	0.764 to 1.021 0.094	0.098
Age at the time of study (m)	1.116	0.967 to 1.284 0.133	0.136
History of fever	2.480	1.190 to 5.222 0.016	0.018
History of cough	1.396	0.642 to 3.049 0.398	0.380
Hemoglobin (g/dL)	0.003	1.100 to 1.515 0.002	0.003

The significant variables were tested for multicollinearity (VIF > 8) between each other and were put into a logistic regression model. Accordingly, fever (P = 0.018) and hemoglobin level (P = 0.003) were found to be the independent predictor for high CRP levels.

4. DISCUSSION

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.[13] 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.[14] Inflammatory biomarkers such as CRP can aid confirm the clinical suspicion of invasive bacterial infection and optimize and tailor antibiotic therapy.[15] However, elevated serum CRP levels have been witnessed in children with acute bronchiolitis in the absence of a confirmed bacterial coinfection or the need of antibiotic used.[16]

Of 200 patients, 120 (60%) were males. Median presentation age was 3.9 (interquartile range (IQR), 1.27-12.33) months. RSV infection predominance in males is well-known but its mechanism has not been explored up till now.[17] This finding might be attributed to the suppression of blood eosinophil cell count or due to the immunosuppressive effect of male hormones. The most common clinical presentation was cough (160 (80%) patients) followed by fever (152 (76%) patients) which is ingoing with the findings of several other studies.[17-20] 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.[19] Median CRP level was 10.5 (IQR, 2.8-35.1) mg/L. CRP was high in 150 (75%) patients. Respiratory syncytial virus (RSV) was detected in 70 patients. 170/200 patients had positive chest X-ray. Antibiotics were used in 140/20 patients. Papoff et al[21] study showed a trend of lower hemoglobin level in infants with severe bronchiolitis compared to those with mild-moderate disease which was in contradictory to their CRP levels.

The significant variables were tested for multicollinearity (VIF > 8) between each other and were put into a logistic regression model. Accordingly, fever (P = 0.018) and hemoglobin level (P = 0.003) were found to be the independent predictor for high CRP levels. 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).[21] Moreover, CRP values had a statistically significant relation with PICU admissions (P = 0:008) in Costa et al.'s study which hypothesized that CRP levels might serve as indirect markers of disease severity.[22] 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.

5. 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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