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Original Research Article

Retrospective Observational Assessment of C-Reactive Protein Levels in Children with Acute Bronchiolitis

Nivedita[1], Sudarshan[2], Animesh Kumar[3]

[1]Senior Resident, Department of Paediatrics , J.L.N.M.C.H, Bhagalpur, Bihar, India
[2]Senior Resident, Department of Paediatrics, J.L.N.M.C.H , Bhagalpur, Bihar, India
[3]Assistant Professor, Department of Paediatrics, J.L.N.M.C.H , Bhagalpur, Bihar, India

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Corresponding author: Dr. Sudarshan
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Abstract

Aim: This study was aimed at assessing the frequency of elevated CRP in children with acute bronchiolitis.

Methods: This was a retrospective observational study where the electronic medical records of all patients with a clinical impression of acute bronchiolitis and were admitted to the pediatric department at JLNMCH, Bhagalpur, Bihar, India 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 (56.66%) patients were males. The most common clinical presentation was cough (115 (76.66%) 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. This study also showed a high overall rate of antibiotic prescriptions in mostly viral disease.

Keywords: Bronchiolitis, Diagnosis, C reactive Protein.

Introduction

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. [1,2] Other agents, such as the parainfluenza virus and some adenoviruses may be found, however. [2] 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. [1]

In terms of complementary diagnostic exams, it is felt that a leukocyte count neither aids diagnosis nor guides treatment of bronchiolitis. [3] Despite the high prevalence of bronchiolitis, there are few data on the efficacy and clinical use of other laboratory exams, particularly measurement of C reactive protein (CRP) level. CRP is the main protein produced in the acute phase of inflammation and abnormal cytokine and protein counts in the acute phase are normally markers of bacteria infection. CRP and cytokine levels can be very high in some cases of viral infection, however. [4] High CRP levels are associated to invasive disease which is not necessarily of bacterial origin. [5]

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 infection [6]. 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 [5,7] 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. [7]

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. [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. [8-10] 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. [8,11,12]

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 at JLNMCH, Bhagalpur, Bihar, India 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.

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. Based on CRP results, patients were divided into two groups, high CRP level (group 1) and normal CRP level (group 2). The two groups were compared in terms of demographic data, clinical presentation (fever and cough), laboratory findings (complete blood count, blood, urine, and CSF cultures, and RSV swab for direct antigen detection and/or PCR, and serology), radiological findings (chest X-ray), antibiotic uses, and the outcomes. 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	85	56.66
Female	65	43.34
Age at presentation (mon), median (IQR)		3.7 (1.27-12.33)
Current age (y), median (IQR)		1.37 (1.14-2.1)
Length of stay (d), median (IQR)		5.0 (3.0-8.0)
Clinical symptoms		
Cough		115 (76.66)
Rhinorrhea		105 (70)
Shortness of breathe		50 (33.34)
Reduced feeding		40 (26.66)
Vomiting		38 (23.33)
Hypoactivity		24 (15)
Sepsis		12 (8)
Cyanosis/Desaturation		12 (8)
Nasal blockage/Congestion		12 (8)
Diarrhoea		12 (8)

85 (56.66%) patients were males. The most common clinical presentation was cough (115 (76.66%) 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

Results of the laboratory investigations are mentioned in the above table.

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
Positive RSV test	30 (30)	14 (8)	0.350
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

Acute bronchiolitis is one of the most common respiratory diseases in children younger than two years of age. In most cases, respiratory syncytial virus (RSV) is the cause. [12] By the age of two, nearly all children are infected at least once by RSV bronchiolitis. [14] It is more common in preterm new borns and in male patients. [15,16]

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. [17] In this study, CRP levels were high in 70% (105/150) of the patients which is comparable to the percentage reported by Lamarão et al. (77.1%). [18] Yet, several studies reported lower percentages, ranging from 1.5% to 62.5%. [10,19] High CRP levels were associated consistently with bacterial infections but inconsistently with viral infections as shown by Peltola et al.'s study. [10]

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. [20]

The most common clinical presentations of patients with acute bronchiolitis in this study were cough (76.66%) and fever (70%), which is ingoing with the findings of several other studies. [18,21,22] 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). [18,22] 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. [12] Nonetheless, majority of children with viral infections have low WBC counts. [10] Moreover, WBC count did not differ between RSV-positive and RSV-negative infants in Resch et al.'s study. [17]

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 RSVpositive (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. [10] 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. [17]

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). [23] 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. [24] 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. [25] 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. and Resch et al.'s studies showed that acute bronchiolitis severity was not influenced by the CRP levels. [17]

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.

References

1. Subcommittee on Diagnosis and Management of Bronchiolitis. Diagnosis and management of bronchiolitis – clinical practice guideline. Pediatrics 2006; 118(4): 1774 -93.
2. Goodman D. Bronchiolitis. In: Behrman, Kliegmam, Jenson. Nelson Textbook of Pediatrics. Saunders 2004:1415 -7.
3. Bordley WC, Viswanathan M, King VJ, Sutton SF, Jackman AM, Sterling L, Lohr KN. Diagnosis and testing in bronchiolitis: a systematic review. Archives of pediatrics & adolescent medicine. 2004 Feb 1;158(2):119-26.
4. Gendrel D, Raymond J, Coste J, Moulin F, Lorrot M, Guerin S, Ravilly S, Lefevre H, Royer C, Lacombe C, Palmer P. Comparison of procalcitonin with C-reactive protein, interleukin 6 and interferon-alpha for differentiation of bacterial vs. viral infections. The Pediatric infectious disease journal. 1999 Oct 1;18(10):875-81.
5. Prat C, Domínguez J, Rodrigo C, Gimenez M, Azuara M, Jiménez O, Gali N, Ausina V. Procalcitonin, C-reactive protein and leukocyte count in children with lower respiratory tract infection. The Pediatric infectious disease journal. 2003 Nov 1;22(11):963-7.
6. Kawasaki Y, Hosoya M, Katayose M, Suzuki H. Correlation between serum interleukin 6 and C-reactive protein concentrations in patients with adenoviral respiratory infection. The Pediatric infectious disease journal. 2002 May 1;21(5):370-4.
7. Toikka P, Irjala K, Juven T, Virkki R, Mertsola J, Leinonen M, Ruuskanen O. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. The Pediatric infectious disease journal. 2000 Jul 1; 19(7):598-602.
8. J. S. Jeon, I. Rheem, and J. K. Kim, "C-reactive protein and respiratory viral infection," Korean Journal of Clinical Laboratory Science, vol. 49, no. 1, pp. 15–21, 2017.
9. Alejandre C, Guitart C, Balaguer M, Torrús I, Bobillo-Perez S, Cambra FJ, Jordan I. Use of procalcitonin and C-reactive protein in the diagnosis of bacterial infection in infants with severe bronchiolitis. European Journal of Pediatrics. 2021 Mar; 180:833-42.
10. Peltola V, Mertsola J, Ruuskanen O. Comparison of total white blood cell count and serum C-reactive protein levels in confirmed bacterial and viral infections. The Journal of pediatrics. 2006 Nov 1;149(5):721-4.
11. Higdon MM, Le T, O'Brien KL, Murdoch DR, Prosperi C, Baggett HC, Brooks WA, Feikin DR, Hammitt LL,

Howie SR, Kotloff KL. Association of C-reactive protein with bacterial and respiratory syncytial virus–associated pneumonia among children aged< 5 years in the PERCH study. Clinical infectious diseases. 2017 Jun 15;64 (suppl_3):S378-86.
12. Fares M, Mourad S, Rajab M, Rifai N. The use of C-reactive protein in predicting bacterial co-Infection in children with bronchiolitis. North American Journal of Medical Sciences. 2011 Mar;3(3):152.
13. Silver AH, Nazif JM. Bronchiolitis. Pediatrics in review. 2019 Nov;40 (11):568-76.
14. Piedimonte G. RSV infections: state of the art. Cleve Clin J Med. 2015 Nov 1; 82(11 Suppl 1): S13-8.
15. Park HW, Lee BS, Kim AR, Yoon HS, Kim BI, Song ES, Kim WT, Lim J, Kim S, Jin HS, Byun S. Epidemiology of respiratory syncytial virus infection in infants born at less than thirty-five weeks of gestational age. The Pediatric infectious disease journal. 2012 Aug 1; 31(8):e99-104.
16. M. Kenneth, Respiratory syncytial virus, in Nelson Textbook of Pediatrics, R. E. Berman and R. M. Kliegman, Eds., WB Saunders, Philadelphia, 16th edition, 2000.
17. Resch B, Gusenleitner W, Müller W. Procalcitonin, interleukin-6, C-reactive protein and leukocyte counts in infants with bronchiolitis. The Pediatric infectious disease journal. 2003 May 1; 22(5):475-6.
18. L. M. Lamarão, F. L. Ramos, W. A. Mello et al., Prevalence and clinical features of respiratory syncytial virus in children hospitalized for community-acquired pneumonia in northern Brazil, BMC Infectious Diseases, 2012;12(1):1–7.
19. Al Harbi S, Kobeisy SA, Hossain OM, Faruqi KM, Sayed BY. Respiratory pathogens in pediatric patients in Saudi Arabia: seasonal variation and epidemiological distribution. Journal of Biomedical Science. 2020;9(4):41.
20. Nagayama Y, Tsubaki T, Nakayama S, Sawada K, Taguchi K, Tateno N, Toba T. Gender analysis in acute bronchiolitis due to respiratory syncytial virus. Pediatric allergy and immunology. 2006 Feb;17(1):29-36.
21. Do Q, Dao TM, Nguyen TN, Tran QA, Nguyen HT, Ngo TT. Procalcitonin identifies bacterial coinfections in Vietnamese children with severe respiratory syncytial virus pneumonia. BioMed Research International. 2020 May 9;2020.
22. Sawatzky J, Soo J, Conroy AL, Bhargava R, Namasopo S, Opoka RO, Hawkes MT. Biomarkers of systemic inflammation in Ugandan infants and children hospitalized with respiratory syncytial virus infection. The Pediatric Infectious Disease Journal. 2019 Aug 1;38(8):854-9.
23. Papoff P, Moretti C, Cangiano G, Bonci E, Roggini M, Pierangeli A, Scagnolari C, Antonelli G, Midulla F. Incidence and predisposing factors for severe disease in previously healthy term infants experiencing their first episode of bronchiolitis. Acta Paediatrica. 2011 Jul;100(7): e17-23.
24. Tavares M, Bonito-Vítor A, Costa S, Rocha R, Guedes-Vaz L. Proteina C Reactiva e gravidade da Bronquiolite aguda. Revista Portuguesa de Pneumologia. 2009;15(1):55-65.
25. Munive A. M., Rosenthalc J. L., Gómez M. S. T., & García D. J. C. A Useful Maneuver to Install Pneumoperitoneum for Laparoscopy in a Frozen Abdomen: Case Report. Journal of Medical Research and Health Sciences. 2022; 5(7): 2083–2090.