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C-Reactive Protein as a Marker of Possible Infectious Complications in Children with Sickle Cell Disease and Fever Admitted to the Hospital

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Abstract

Background: To determine if c-reactive protein (crp) can predict possible bacterial infections in children with sickle cell disease (SCD) and fever who are admitted to the hospital.

Methods: Retrospective chart review of children age 0 - 18.9 year old with SCD admitted to the hospital with fever and who had crp measured. Age, maximum temperature, white blood count (WBC), absolute neutrophil count (ANC), percent of neutrophils (ANC/WBC), and crp were evaluated.

Results: 96 cases met inclusion criteria. 21 (22%) cases had possible bacterial infection. Compared to children without possible bacterial infections, children with possible bacterial infections were older (10.1 vs. 5.2 yr, p = 0.022), had higher crp (5.9 vs. 1.8 mg/dL, p = 0.005), higher WBC (21.1 vs. 16.0 x 10^3/mm^3, p = 0.009), and higher ANC (13.8 vs. 8.8 x 10^3/mm^3, p = 0.004). A receiver operator characteristic (ROC) curve using crp and age produced an area of 0.86.

Conclusions: A low crp, especially in a younger child, may identify patients at low risk for serious bacterial infection. Prospective use of crp in this population, including outpatients, is warranted in order to identify the best sensitivity and specificity for predicting possible bacterial disease.

Keywords: C-reactive protein; Sickle cell disease; White blood count

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Introduction

Children with sickle cell disease (SCD) are at increased risk of invasive bacterial disease from encapsulated organisms compared to children without SCD. This is primarily due to the splenic dysfunction that accompanies SCD. Because of the potential mortality associated with bacteremia, children with SCD and fever are recommended to undergo prompt evaluation, including a physical exam, complete blood count, blood and urine cultures, and sometimes chest x-ray. These children often receive empiric parenteral antibiotics until blood cultures show no bacteremia for forty-eight hours. Studies have identified clinical and laboratory features that are associated with low rates of bacteremia or that predict bactermia in this population [1,2]. Recent reviews have shown a decrease in the rate of bacteremia in children with SCD compared to historical data, likely due to the introduction of vaccines for *H. influenza* and *S. pneumonia* [3,4]. C-reactive protein (crp) is an acute phase reactant that has been studied as an indicator of bacterial infection in a variety of clinical situations [5-8]. It is common at our institution for resident physicians to order reflexively a crp on children admitted to hospital with fever. This practice prompted us to review its use in our patients. Crp has not been evaluated as a predictor of bacterial infection in children with SCD and fever. Identification of new markers for bacterial disease may help clinicians appropriately respond to those children at highest risk for morbidity/mortality or identify patients with lower risk for serious bacterial infections.

Methods

This retrospective study was approved by the IRB which waived the requirement for informed consent based on impractibility. The records of children admitted to Baystate Children's Hospital between January 1, 2009 and December 31, 2012 with a diagnosis of SCD (homozygous SS, SC, or $S\beta^{0/+}$ thalassemia), a report of fever in the admission note, and who had crp tested at presentation

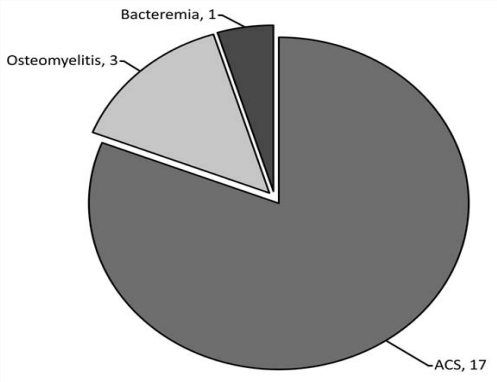

Figure 1: Distribution of infections.

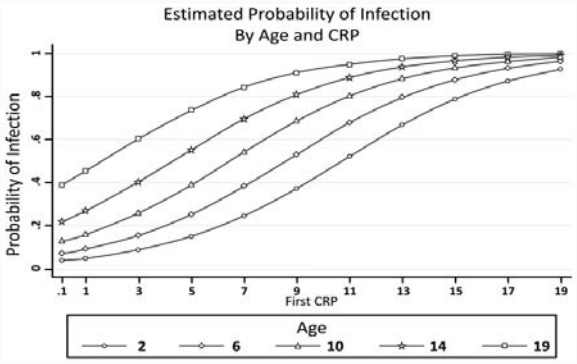

Figure 2: Estimated probability of bacterial infection by age and crp.

were included. Because evaluation and treatment for fever in this population is often initiated with only a parent's report of fever, there were no criteria for what constituted a fever or requirement that a fever was documented. Data on presenting signs/symptoms, age, gender, initial total white blood count (WBC), absolute neutrophil count (ANC), crp, antibiotic treatment, culture results, and imaging studies were collected. Bacterial disease/ possible bacterial disease was defined as a diagnosis of bactermia, pyelonephritis, pneumonia and osteomyelitis. Because bacterial pneumonia can be a cause of the acute chest syndrome (ACS), all cases of ACS were categorized as an infectious complication. Pneumonia was defined as a new infiltrate on plain radiographic imagining.

Per institutional practice, children age 0–5 years had been prescribed a daily prophylactic antibiotic. Immunization schedule was managed by children's primary pediatrician but was not confirmed at time of chart review.

Univariable comparisons of case and comparison groups (i.e., case status) were conducted using t-tests for unequal variances for continuous outcome and Fisher's exact test for categorical outcomes. For multivariable analyses, logistic regression was used to examine the relationship between first crp (crp1) and case status, accounting for age, maximum temperature, WBC, ANC, and the ratio of ANC to WBC. A final model was produced by removing variables that did not contribute meaningfully to the model ($p > 0.25$). Receiver operating characteristic (ROC) curve were generated for each model to estimate the ability of the model to distinguish cases from non-cases. ROC curves for the models were compared using the approach by Delong, Delong and Clarke-Pearson 9. All analyses were conducted in Stata (ver. 12.1, College Station, TX).

Table 1: Clinical and Laboratory characteristics of Children With or Without Presumed Bacterial Infection.

Clinical/Lab Characteristic	Presumed Bacterial Infection (n=21)	Control Group (n=75)	P
	Mean (sd)	Mean (sd)	
Male, n (%)	17 (18.1)	50 (66.7)	0.29[a]
Age (yrs)	10.1 (6.1)	5.2 (5.6)	0.002
Max. temp. (°C)	39.4 (0.6)	39.3 (0.8)	0.91
SS/Sβ$^{0/+}$, n (%)	20 (95.2)	64 (85.3)	0.45
Crp 1 (mg/dL)	5.9 (5.9)	1.8 (2.3)	0.005
Crp 2[b] (mg/dL)	6.3 (4.4)	2.5 (2.4)	0.008
WBC (x10^3/mm^3)	21.1 (7.6)	16.0 (6.3)	0.009
ANC (x10^3/mm^3)	13.8 (6.7)	8.8[c] (5.4)	0.004
ANC/WBC	63.2 (14.2)	52.7[c] (18.9)	0.008

[a]Fischer's exact test.
[b]case n = 14, control n = 40,
[c]control = 74.

Results

128 episodes among 35 patients were identified. Crp was not obtained at presentation in 32 episodes, leaving 96 episodes for evaluation.

21 children (22%) were classified as having a serious infectious complication (Figure 1). One child had culture proven bacteremia with Strep pneumonia. Three children had clinical and radiographic findings consistent with osteomyelitis, the diagnosis supported by infectious disease specialty consultation. Blood cultures were negative in these patients and cultures of affected bone were drawn more than 24 hours after the initiation of parenteral antibiotics and were negative; the children were treated empirically for osteomyelitis. 17 children were diagnosed and treated for pneumonia based on clinical and radiographic findings; blood cultures in these patients were negative.

Children with serious infectious complications were significantly older, had higher mean initial WBC, ANC, ANC/WBC, and crp levels than children without bacterial infection (Table 1).

54 children had a second crp drawn at least 8 hours after the initial crp (14 in the possible bacterial infection group, 40 in the non-bacterial infection group). The mean of the second crp was higher in the possible bacterial infection group than in the non-bacterial group (Table 1).

Receiver Operator Curve (ROC) using the first crp alone gave an area under the curve of 0.75 (95% CI: 0.61, 0.89). The value of crp in this model that maximized sensitivity and specificity was 1.8mg/dL (crp ≥ 1.8mg/dL yielded a sensitivity of 70.6% and a specificity of 73.0%). ROC areas were generated for crp in conjunction with each of the other variables (Table 2). Because crp and age yielded the greatest area, these variables were used to create a model to determine the probability of bacterial infection for different ages (Figure 2).

All patients received at least one dose of parenteral antibiotics.

Discussion

Crp is an acute phase reactant that increases in a variety of inflammatory conditions, including bacterial infection. It has been used a potential marker for serious infections in several clinical situations. In this series, children with SCD who presented with fever

Table 2: Receiver Operator Curve (ROC) areas for crp in conjunction with other variables.

Model	ROC area	95% CI
Crp alone	0.75	0.61, 0.89
Crp *and* Age	0.84	0.75, 0.93
WBC	0.74	0.61, 0.87
ANC	0.75	0.62, 0.87
ANC/WBC*	0.75	0.62, 0.87

Crp: C-reactive Protein; WBC: Total White Blood Count; ANC: Absolute Neutrophil Count.
*N = 95

and were ultimately diagnosed with a serious infectious complication had higher mean crp than those without a diagnosis of an infectious complication. Use of crp alone as a screening test in this situation yields an ROC area consistent with a "fair" screening test. The addition of age as a variable to crp increases the ROC area to that of a "good" screening test.

This study has certain limitations. Crp may not rise for several hours after a bacterial infection is present. We evaluated the operating characteristics of the first crp drawn, as this is what would be used when trying to make an initial risk determination. If a child had blood work done very soon after fever was detected, it is possible that crp would not have had adequate time to rise. For the cases in which two crp's were drawn at least 8 hours apart, the means of the first and second crp values were not significantly different within each group (possible infected group: mean first crp 5.9, mean second crp 6.3, p = 0.85; non-infected group: mean first crp 1.8, mean second crp 2.5, p = 0.12). This argues that an initial crp more often than not reflects the presence (or absence) of inflammation by the time of presentation.

Only children admitted to the hospital were included. Although it is likely that children seen and discharged from the emergency room or clinic with fever did not ultimately have serious bacterial illness, this cannot be assumed. Data for these febrile patients treated as outpatients were not included, thus potentially affecting the operating characteristics of crp. A recent study by Baskin et al, however, suggests that the clinical and lab features of children with SCD admitted to the hospital for fever are similar to those treated as outpatients [4].

The classifying of all cases of ACS as bacterial pneumonia most likely altered the operating characteristics of crp. In addition to bacterial pneumonia, ACS may be associated with primary pulmonary sickling, fat embolism, or a number of respiratory viruses. However, because a bacterial infection as the cause of an episode of ACS may not be provable without more invasive procedures (e.g. bronchoscopy), the true number of bacterial disease within ACS is unknown in routine clinical practice. Causes of ACS apart from bacterial penumonia are also associated with inflammation, further complicating interpretation of an elevated crp in a child with SCD, fever, and pulmonary infiltrate. The mean crp for the 17 ACS cases was 4.8, still significantly above the mean for non-infected cases (1.8, p = 0.001), but not quite significantly lower than the four infected cases without a diagnosis of pneumonia/ACS (10.8, p = 0.06).

One interesting finding is that children with possible bacterial disease were older than those without. This may be because younger children tend to get more febrile viral illnesses than older ones, thus lowering the mean age of the group without bacterial disease. Additionally, a significant number of cases of ACS occur in patients between 10 and 19 years old, about 27% in one study [10]. The mean age of cases of ACS in our population was 11.9 years and their categorization as bacterial disease likely increased the mean age of this group. When cases of ACS were excluded, mean crp remained significantly elevated in the possible infected group compared to the non-infected group (10.8 vs. 1.8, p <0.0001). The mean age of the possible infected group then fell to 2.6 years and was not significantly different from the non-infected group (p=0.34). Numbers in this infected subgroup were very small (N = 4) and results must be viewed with caution.

Because parental report of fever was allowed, in some instances there was no objective documentation of fever. In our experience, however, parental report of fever in this population is almost always accepted and is used to initiate an evaluation for bacterial infection. Thus, the study reflects what is practiced clinically.

Despite the statistically significant increase in crp in possible bacterial infection, it is unclear if any crp value would alter initial management for fever in this population. In this series, the vast majority (20 of 21, 95%) of children diagnosed with possible bacterial illnesses had signs of infection, such as localized swelling over a bone (subjects with osteomyelitis), or chest pain, tachypnea, shortness-of-breath, or hypoxia (pneumonia/ACS). Only a 13 month old with *S. pneumonia* bacteremia had no clinical signs of illness other than fever. This child had a crp and WBC in the top quartile for possible infected children. The crp would have been in the 98th percentile and WBC in the 90th percentile for non-infected children. The repercussions of not treating a potentially bacterially infected child, however, makes the determination of an acceptable cut-off value for crp problematic. It may be, however, that as more data using crp in this population are generated, a value may be identified below which the chance of bacterial infection is so low that oral antibiotics alone or even observation is acceptable.

Children with SCD hospitalized for fever and diagnosed with possible bacterial illness have higher mean crp compared to those without bacterial illness. Given the reported decrease in the frequency of bacteremia in children with SCD, identification of additional predictors of bacterial infection may help guide management. Because children with SCD and fever will usually receive empiric parenteral antibiotics - and the repercussions of a missed bacterial illness are great - using crp to determine initial antibiotic administration is likely limited at this time. A very low crp, especially in a younger child with no localizing signs of infection, may be helpful to determine patients who are candidates for early discharge or those who can be managed as an outpatient. Our results indicate that a larger, prospective study of crp for fever in this population, including outpatients, is warranted in order to identify best sensitivity and specificity.

References

1. Wilimas JA, Flynn PM, Harris S, et al. A Randomized Study of Outpatient Treatment with Ceftriaxone for Selected Febrile Children with Sickle Cell Disease. New Eng J Med. 1993; 329: 472-476.

2. West DC, Andrada E, Azari R, Rangaswami AA, Kuppermann N. Predictors of Bacteremia in Children With Sickle Cell Disease. J Pediatr Hematol Oncol. 2002; 24: 279-283.

3. Narang S, Fernandez ID, Chin N, Lerner N, Weinberg GA. Bacteremia in Children with Sickle Hemoglobinopathies. J Pediatr Hematol Oncol. 2012; 34: 13-16.

4. Baskin MN, Goh XL, Heeney MM, Harper MB. Bacteremia Risk and Outpatient Management of Febrile Patients with Sickle Cell Disease. Pediatrics. 2013; 131: 1035-1041.

5. Pulliam PN, Magdy W, Attia MW, Kathleen M, Cronan KM. C-Reactive Protein in Febrile Children 1 to 36 Months of Age With Clinically Undetectable Serious Bacterial Infection. Pediatrics. 2001; 108: 1275-1279.

6. Shaoul R, Lahad A, Tamir A, Lanir A, Srugo I. C reactive protein (CRP) as a predictor for true bacteremia in children. 2008; 14: CR255-261.

7. Tudela P, Prat C, Lacoma A, Model JM, Dominguez J, Gimenez M, et al. Biological markers for predicting bacterial infection, and severity of infection in the emergency department. Emergencias. 2012; 24: 348-356.

8. Dae Yong Kim, Yoon-Seon Lee, Shin Ahn, Yeon Hee Chun, Kyung Soo Lim. The Usefulness of Procalcitonin and C-Reactive Protein as Early Diagnostic Markers of Bacteremia in Cancer Patients with Febrile Neutropenia. Cancer Res Treat. 2011; 43: 176–180.

9. DeLong, ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics. 1988; 44: 837–845.

10. Vichinsky EP, Neumayr LD, Earles AN, Williams R, et al. Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease. New Eng J Med. 2000; 342: 1855-1865.