

Usefulness of the C-Reactive Protein in Predicting the Need for Antibiotics Among Febrile Inpatients with Sickle Cell Disease[§]

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Abstract: *Objective:* To determine whether the C-reactive protein (CRP) can help identify which febrile patients with sickle cell disease (SCD) require antibiotic therapy.

Patients and Methods: We performed a chart review of patients with SCD (including S-S, S-C, and S-Thal) admitted to the hospital with fever [temperature >38.3°C <2 years of age; >38.9°C ≥2 years of age] over a thirty-month period (July 2009 – December 2011). Data extracted included temperature, age, high sensitivity CRP value, chest x-ray and culture results, and the underlying cause of fever, categorized as bacterial (antibiotics necessary) or non-bacterial (antibiotics not necessary). The Mann-Whitney U-test was then used to compare the median CRP levels of patients requiring antibiotics versus those whose illnesses did not require antibiotic treatment.

Results: Fifty-four febrile patients with SCD were admitted to the hospital. Nineteen had final diagnoses that required antibiotic treatment and their median CRPs were significantly higher than the thirty-five who had diagnoses that did not meet the requirements for antibiotic treatment (100.9 mg/L vs 17.3 mg/L, $p < .001$). All patients who needed antibiotics had a CRP >39 mg/L.

Conclusion: The current data indicate that among febrile patients with SCD, the CRP may help differentiate bacterial infections which require antibiotic treatment from other diseases for which antibiotics are not necessary. Our data suggests that there may be a level of CRP below which a bacterial etiology is unlikely.

Keywords: C-reactive protein, fever, sickle cell disease.

INTRODUCTION

Patients with sickle cell disease (SCD) often require hospitalization for a number of complications, including vasoocclusive crisis (VOC), acute chest syndrome (ACS)/pneumonia, aplastic crisis, splenic sequestration, bacteremia, and osteomyelitis. These conditions may have similar clinical presentations, including fever, bone pain, and/or respiratory distress. Therefore, early in the clinical course of an acute illness, it may be difficult to distinguish among these entities and choose the most appropriate initial therapy.

It is well known that patients with SCD are at an increased risk for overwhelming systemic bacterial infections with *S. pneumoniae*, *H. influenzae*, *N. meningitidis*, and *Salmonellae* [1, 2]. Current guidelines suggest treating with broad spectrum antibiotics any child with SCD who presents with a fever >38.3-38.9°C (>101-102°F) [3, 4] At the same

time, there is a growing concern about antibiotic overuse, so that many institutions have instituted antibiotic stewardship programs [5].

At present, there are no easily obtained, and consistently reliable, laboratory examinations that distinguish between patients who have VOC or a non-bacterial illness (do not require antibiotics) from those with bacteremia, sepsis, ACS/pneumonia, osteomyelitis, or other diagnoses for which antibiotics are necessary. Inflammatory markers that have been studied include the erythrocyte sedimentation rate (ESR), which is typically low in patients with SCD as the cells do not form rouleaux [6] The ESR may increase during both painful crises and infections, but it does not reliably differentiate between the two [7]. West *et al.* [8] showed that there are significant increases in white blood cells, absolute neutrophil, and absolute band counts when comparing SCD patients with and without bacteremia. However, there were too few episodes of bacteremia to determine reliable cut-offs. In contrast, secretory phospholipase A2 is an accurate test for identifying present or incipient ACS in young patients who were present to the emergency department with VOC, although it is not in widespread use [9]. Procalcitonin is a sensitive inflammatory marker, however data is insufficient to conclude that an elevation reliably identifies children with SCD who have bacterial infections [10].

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A readily available marker of systemic inflammation is the C-reactive protein (CRP), named for its ability to form a precipitate with polysaccharide C of *Streptococcus pneumoniae*. It is an exquisitely sensitive acute phase reactant that has gained wide acceptance as an indicator of systemic inflammation [11]. There is recent evidence that the CRP is elevated in VOC [12], although there are limited data regarding the reliability of the CRP for discriminating between VOC and other critical illnesses in patients with SCD and fever. Therefore, a more comprehensive understanding of the CRP in SCD may potentially aid in addressing the clinical dilemma of distinguishing VOC from other entities requiring antibiotics.

METHODS

We performed a chart review of patients with SCD (including S-S, S-C, and S-Thal) who were admitted to the Jacobi Medical Center with fever over a thirty-month period (July 1, 2009 through December 31, 2011). Data extracted included temperature, age, high sensitivity CRP value, culture and chest-ray results (if obtained), and the underlying cause of fever, categorized as bacterial (antibiotics necessary) and non-bacterial (antibiotics not necessary). The study protocol was approved by the IRB of both the Albert Einstein College of Medicine and the New York City Health and Hospitals Corporation.

Subjects

Inclusion criteria: Febrile patients 3 months to 24 years of age with SCD (S-S, S-C, S-Thal) were eligible if a CRP and, at a minimum a blood culture, were obtained as part of the emergency department work-up prior to admission to the inpatient unit.

Exclusion criteria: Patients were excluded if they had received antibiotics during the previous five days (except for prophylactic penicillin) and/or a blood transfusion during the previous three months.

Fever

Fever was defined as a temperature $>38.3^{\circ}\text{C}$ (patients <2 years of age) or a temperature $>38.9^{\circ}\text{C}$ (patients ≥ 2 years of age).

Diagnoses Definitions

Bacterial infections: Patients were classified as having a bacterial illness if a bacterial culture (blood, urine, stool) was positive for a known pathogen. Diagnoses included ACS/pneumonia, bacteremia, sepsis, osteomyelitis, pyelonephritis, bacterial enteritis, and cellulitis. The diagnosis of ACS/pneumonia required the presence of a new infiltrate on a chest x-ray that was interpreted by a pediatric radiologist. The diagnosis of osteomyelitis was confirmed by MRI results.

Non-bacterial illnesses: Patients were classified as having a non-bacterial illness if all bacterial cultures (blood, urine, stool), and a chest x-ray, if obtained, were negative. Diagnoses included VOC, viral syndrome, asthma/bronchiolitis, splenic sequestration, aplastic crisis, and gastroenteritis.

CRP

High sensitivity CRP was measured using commercially available immunoturbidimetric methods and the 67-Integra machine. Reagents containing latex particles coated with mouse or rabbit anti-CRP antibodies were mixed with the patient's sample. The subsequent precipitate was analyzed for decreased intensity of light. The reference range for patients >2 months of age was 0.1-2.8 mg/L.

Data Analysis

We compared the median CRP values between febrile inpatients that truly required antibiotics for diagnoses of bacteremia, sepsis, ACS/pneumonia, osteomyelitis, and urinary tract infection versus febrile inpatients who ordinarily would not require antibiotic therapy for their diagnoses (VOC, aplastic crisis, splenic sequestration, and viral illnesses). Anderson-Darling tests revealed that while the median CRPs of the antibiotics required patients had a normal distribution ($p < 0.1795$), the antibiotics not required cohort did not have a normal distribution ($p < .0005$). Therefore, the Mann-Whitney U-test was used to compare median CRP levels between these groups.

RESULTS

There were a total of fifty-four febrile episodes among forty-five different patients. Nine patients were admitted twice; two required antibiotics during both admissions, four required antibiotics during one admission, and three did not require antibiotics during either admission. As shown in Table 1, there was no significant difference in age or gender distribution between the two groups. However, nineteen inpatients had final diagnoses that required antibiotic treatment and their median CRPs were significantly higher than the thirty-five inpatients who did not need antibiotics [CRP = 100.9 mg/L (IQR 82.9) *vs* CRP = 17.3 mg/L, $p < 0.001$ (IQR 47.7)].

As shown in the box plot (Fig. 1), every patient who required antibiotics had a CRP level >39 mg/L.

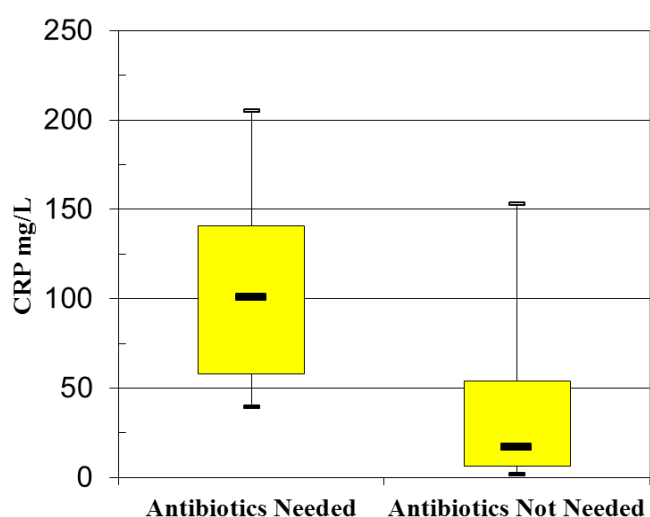
DISCUSSION

The CRP has been studied as a diagnostic tool in a variety of illnesses. In the pediatric population, CRP has been utilized in diseases such as Kawasaki disease [13], asthma [14], appendicitis [15], and neonatal sepsis [16]. Recently, an elevation of the CRP has been noted in children with SCD during episodes of vasoocclusive crisis [17].

Distinguishing VOC from other SCD complications, including those requiring antibiotics, remains a clinical dilemma. Our findings suggest that CRP levels may provide additional guidance when the etiology of a patient's pain or fever is ambiguous. Specifically, these data indicate that the CRP may aid in distinguishing bacterial infections (antibiotics necessary) from presumed viral infections (no antibiotics needed) in febrile patients. Our results suggest that for febrile patients with SCD, there may be a level of CRP below which a bacterial etiology is unlikely. Further prospective study with larger numbers of patients is therefore necessary to confirm whether the CRP is a reliable predictor of a bacterial illness.

Table 1. Comparison of patients who did and did not require antibiotics.

	Antibiotics Necessary	Antibiotics Not Necessary
Number of Patients	19	35
Age Mean (months) ± SD	116.8 ± 77.5	78.1 ± 74.1 ¹
Gender (male/female)	8/11	23/11 ¹
CRP Median (IQR)	100.9 (51.9,140.8)	17.3 (6.3, 54.0) ²
CRP Range	39.2-204.8	0.7-142.3
Hemoglobin		
S-S	11	29
S-C	5	5
S-Thal	3	1
Final Diagnoses		
ACS/pneumonia	9	
Bacteremia/sepsis	4	
Osteomyelitis	2	
Pyelonephritis	2	
Bacterial enteritis	1	
Cellulitis	1	
VOC		18
Viral syndrome		9
Asthma/bronchiolitis		3
Splenic sequestration		3
Aplastic crisis		1
Gastroenteritis		1

¹ p = NS.² p < .001.**Fig. (1).** Comparison of CRP levels between patients who did and did not require antibiotics.

LIMITATIONS

The present study has a number of important limitations. 1) The data was collected retrospectively and may therefore reflect errors or omissions in the electronic records. 2) We

report on a relatively small number of patients, so it is possible that a few outlier results may affect the findings and conclusions. 3) We had too few patients to stratify the data based on type of hemoglobinopathy, bacterial organism identified, and final discharge diagnosis.

ABBREVIATIONS

ACS = Acute chest syndrome
 CRP = C-reactive protein
 SCD = Sickle cell disease
 VOC = Vasooclusive crisis

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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