CLINICAL VALUE OF PROCALCITONIN FOR DIFFERENTIATION OF INFECTION AND ACTIVE JUVENILE IDIOPATHIC ARTHRITIS

A Thesis

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by

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ABSTRACT

Background: Patients with juvenile idiopathic arthritis (JIA) often present with signs and symptoms suggestive of serious bacterial infection (SBI). However, it is a challenge to differentiate infectious from non-infectious presentation in routine clinical care. Procalcitonin (PCT) is a serum biomarker that is elevated in the setting of SBI, but whether it can reliably differentiate infection from disease flare in patients with JIA is unknown.[1] We conducted a prospective cohort study to test the hypothesis that PCT levels will differ between active JIA, quiescent JIA, and bacteremic patients and healthy controls.

Methods: From 10/16-4/18, consecutive children 6 months - 18 years of age with a) active untreated JIA (=>4 inflamed joints) b) quiescent JIA and c) healthy elective pre-surgical candidates were recruited from clinics at a musculoskeletal specialty hospital. JIA was defined according to ILAR criteria. Patients with active JIA despite treatment were excluded, to avoid confounding by treatment. Clinical data and serum samples from children with active and quiescent JIA meeting the same criteria were included from a prior study. Consecutive bacteremic patients were identified from an associated pediatric intensive care unit over the same period. No matching was performed. PCT as well as other common measures of inflammation were measured. Descriptive statistics and univariate logistic analyses were performed as appropriate using SAS version 9.4. The study was IRB approved.

Results: Bacteremic patients were younger than patients in the other three groups (median age 2.1 vs. 14.0 years) and had a variety of infections. ESR, CRP, and PCT were all elevated in bacteremic patients in comparison to the other groups. ESR and CRP both had wide ranges that overlapped between groups; however, the PCT concentration exceeded 0.15ug/mL in 0 out of 27 patients with active JIA and 1 out of 32 patients with quiescent JIA, while it was <= 0.15ug/mL in only 1 bacteremic patient. PCT did not differ between patients with active and quiescent JIA.

Conclusions: Our study indicates that serum ESR, CRP, and PCT levels are all biomarkers that can be used to distinguish SBI vs. active JIA at presentation. However, PCT is the most accurate, with the least overlap between patients with infection and non-infectious inflammatory arthritis. This finding can help clinicians direct therapy. However, PCT is not a useful biomarker to assess disease activity in JIA. Further studies are needed to assess whether measurement of serum PCT is useful in differentiating JIA flares from less severe infections.

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BIOGRAPHICAL SKETCH

Since I was in high school, I have wanted to go to medical school and become a doctor. I slowly pursued that dream by completing all the pre-medical requirements at Barnard College, taking the MCAT, and applying to medical school. Once I was in medical school at Albert Einstein College of Medicine, I first became aware of my interest in rheumatology during the first two years of classroom courses, and then for pediatrics, during the clinical rotations. I decided to pursue a career in pediatric rheumatology, and I have been extremely satisfied with my choice. As I have progressed through the various stages of my medical education, my vision for my career has become more clear.

During medical school and residency at NYU Langone Medical Center/Bellevue Hospital Center, I was fortunate to have the opportunity to refine my ideas of what I was interested in. I always knew that I enjoyed clinical work and taking care of patients. But during medical school, I took a year to do research, and I worked with multiple researchers in the Division of General Pediatrics at Montefiore. I contributed to many projects, ranging from care of neonates to use of Hydroxyurea in sickle cell disease. I was engaged in multiple aspects of the research, including qualitative interviews and transcript review, organization of data, statistical analysis, and writing manuscripts. I found this work extremely rewarding, and it appealed to me in two ways. First, I enjoyed the analysis, problem solving, and brainstorming and felt that it utilized a very different part of my brain from the clinical care to which I had become accustomed. Second, it was rewarding, and I enjoyed the idea that I could make a

difference not only to my patients, but that I could effect changes in management for many more providers and patients in the future based on my research work.

Throughout my fellowship at Weill Cornell Medicine/Hospital for Special Surgery, I have engaged in clinical and translational research. I have conducted a prospective cohort study to evaluate (1) procalcitonin as a biomarker for differentiation of infection and disease activity in children with juvenile idiopathic arthritis, and (2) the value of Patient Reported Outcome Measurement Information System Computer Adaptive Tests (PROMIS CATs) in children with JIA. I have presented some of my work at national conferences, and have thoroughly enjoyed these experiences. I also won the Charles L. Christian Award for Excellence in Musculoskeletal Research at the completion of my fellowsip. In addition, I am currently enrolled in the Weill Cornell Clinical and Translational Science Center Master's Program for Clinical and Translational Investigation. This exciting opportunity has allowed me to continue to build my skills and knowledge about research.

At this point, I feel lucky to have a solid sense of what I want for my career, as well as the resources and mentors to help me get there. I enjoy working with patients, and will continue to do that. I also look forward to the opportunity to engage in research for a significant part of my effort, in order to help further evidence-based medicine and treatment in pediatric rheumatology. I look forward to continuing to pursue these goals, with the foundation that I have developed through the Weill Cornell Clinical and Translational Science Center Master's Program for Clinical and Translational Investigation.

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Finally, I would like to acknowledge my family and friends who helped me get here, especially my mother; my father, my ultimate mentor; and my wonderful daughter, Elinor.

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LIST OF ABBREVIATIONS

ANA = anti-nuclear antibody

ANOVA = analysis of variance

CBC = complete blood count

CHAQ = Childhood Health Assessment Questionnaire

CRP = C-reactive protein

ESR = erythrocyte sedimentation rate

ILAR = International League Against Rheumatism

IRB = Institutional Review Board

JADAS = juvenile arthritis disease activity score

JIA = juvenile idiopathic arthritis

NSAIDs = non-steroidal anti-inflammatory drugs

PCT = procalcitonin

BACKGROUND

Juvenile Idiopathic Arthritis (JIA) is a chronic autoimmune disease that affects approximately 300,000 children in the United States.[1] Monitoring of disease activity relies upon history, physical examination, and laboratory data. However, because of overlapping features between JIA and various complications, diagnosis and management can be difficult, both at disease onset and during disease flares. Many studies have been done with the goal of finding new biomarkers for monitoring of disease activity and complications in JIA, based on basic science research and clinical studies in adult patients.[2,3,4] However, few studies have yielded positive results, and the key diagnostic challenges persist.

One specific situation that requires better objective data is the diagnosis of infection versus flare in JIA. This distinction is often hampered by diagnostic uncertainty, patient age, and administration of chronic immunosuppressive therapy. The evaluation and management for infection carries significant morbidity and often delays the initiation of appropriate anti-rheumatic treatment. Therefore, distinguishing between these two entities is of great clinical importance. However, no clear biomarkers have been found to accomplish this goal.

Procalcitonin (PCT) is a molecule that is consistently elevated in bacterial infection.[5,6]

PCT is typically secreted by C cells of the thyroid, and then cleaved to calcitonin.[7] During stress, PCT secretion is elevated by multiple mechanisms: (1) excessive production, (2) decreased cleavage to calcitonin, and (3) extra-thyroidal transcription and synthesis. There is evidence indicating that this occurs exclusively in bacterial infections.[8,9]

Few studies have examined this biomarker in children with chronic inflammatory disease. The utility of PCT has been evaluated in Kawasaki disease and Henoch Schonlein purpura.[10,11[The performance of PCT to distinguish increased disease activity from bacterial infection is unknown in children with JIA. Therefore, this prospective cohort study was designed to test that the hypotheses that (1) PCT can distinguish infection from active disease in JIA, and (2) PCT will differentiate between active and quiescent disease in children with JIA.

METHODS

Patient Population

Between 10/2016 and 5/2018, four groups of consecutive children aged 1 to 18 years were recruited from a single academic center during a standard of care visit:

a) Active JIA
b) Quiescent JIA
c) Children without rheumatic disease undergoing elective surgery
d) Children with bacteremia admitted to the pediatric intensive care unit

JIA was defined according to ILAR criteria.[12] Active JIA was defined as incident cases untreated with anything besides NSAIDs, and ≥4 inflamed joints; quiescent JIA was defined as prevalent treated cases, with <4 inflamed joints, and stable treatment for ≥1 month. Exclusion criteria included: (1) non-English speaking patients/parents because some of the disease assessment tools utilized in this study are only validated in English; (2) patients with oligoarticular type JIA; (3) patients with systemic onset JIA; (4) patients with active JIA despite treatment to minimize confounding by treatment; (5) patients with other rheumatologic diagnoses; (6) patients with primary

renal disease; (7) patients taking stimulant medications because these drugs can affect PCT levels[13,14]; and (8) patients with current infection. Inclusion and exclusion criteria for surgical controls and bacteremic patients can be found in the supplemental criteria.

Data Collection

The following information was collected for each patient: JADAS-71 scores [score 0-101, including swollen joint count, physician global health assessment, patient global health assessment, and modified erythrocyte sedimentation rate (ESR)]; Childhood Health Assessment Questionnaire (CHAQ); relevant laboratory data [complete blood count (CBC), ESR, C-reactive protein (CRP), and PCT]. All labs were processed at a single standard study laboratory. This study was approved by the Hospital for Special Surgery and Weill Cornell Medicine IRBs.

Statistical Analysis

PCT and ESR, CRP, and hemoglobin were compared between groups. Continuous variables were compared using ANOVA or Wilcoxon rank-sum test, and categorical variables were compared using Fisher's exact test.

RESULTS

Patient characteristics of all four groups are summarized in Table 1. Most groups had a median age of 13-14 years, although bacteremic patients were younger than the other groups (median age 2.1 vs. 14.0 years). Most groups were predominantly White or Caucasian, except for the bacteremic patients, who were more racially diverse.

JIA characteristics of our patient groups are further characterized in Table 2. Both the active and quiescent groups had a mix of JIA subtypes. Because active JIA were defined as incident, disease duration was significantly shorter in this group than in the children with quiescent, prevalent JIA. Overall, approximately 47% of our patients were positive for ANA, while fewer patients were positive for other autoantibodies and disease markers of known significance.

Laboratory values for all study participants are summarized in Table 3. ESR, CRP, and PCT were all elevated in bacteremic patients in comparison to the other groups. ESR and CRP both had wide ranges that overlapped between groups (Figure 1 and 2); however, the PCT concentration exceeded 0.15ug/mL, the standard cutoff for suspicion for infection in 0 out of 27 patients with active JIA and 1 out of 32 patients with quiescent JIA, while PCT concentrations exceeded this level 16 out of 17 bacteremic patients (Figure 3). PCT did not differ between patients with active and quiescent JIA. Based on this data, sensitivity and specificity for PCT and infection were 94.1% and 98.3% (Table 4), and positive predictive value and negative predictive value were 94.1% and 98.3%.

Table 1. Patient characteristics

	Active Untreated JIA (n = 27)	Quiescent JIA (n = 32)	Healthy Controls (n = 16)	Bacteremic Patients (n = 17)
Age, years (median, IQR)	13.0 [7.0, 16.0]	14.0 [10.8, 15.4]	14.4 [13.9, 15.5]	2.1 [0.8, 8.8]
Sex				
Male	11 (40.7%)	5 (15.6%)	6 (37.5%)	10 (58.8%)
Race				
Caucasian/White	20 (74.1%)	30 (93.8%)	12 (75.0%)	5 (29.4%)
AA/Black	3 (11.1%)	0 (0.0%)	3 (18.8%)	4 (23.5%)
Asian	3 (11.1%)	1 (3.1%)	0 (0.0%)	3 (17.7%)
Other	1 (3.7%)	1 (3.1%)	1 (6.3%)	5 (29.4%)
Ethnicity				
Hispanic	0 (0%)	4 (12.5%)	1 (6.3%)	1 (5.9%)

Table 2. JIA disease characteristics

	Active and quiescent JIA (n=59)	Active JIA (n=27)	Quiescent JIA (n=32)
JIA category			
Polyarticular	14 (23.7%)	6 (22.2%)	8 (25.0%)
Psoriatic	12 (20.3%)	6 (22.2%)	6 (18.8%)
Spondyloarthropathy	33 (56.0%)	15 (55.6%)	18 (56.2%)
Disease duration (mean)	6-12 months	3-6 months	2-3 years
ANA+	28 (47.4%)	10 (37.0%)	17 (53.1%)
B27+	11 (18.6%)	4 (14.8%)	16 (50.0%)
RF+	4 (6.8%)	2 (7.4%)	13 (40.6%)
CCP+	8 (13.5%)	4 (14.8%)	11 (34.4%)

Table 3. Laboratory values

	Active Untreated JIA (n = 27)	Quiescent JIA (n = 32)	Healthy Controls (n = 16)	Bacteremic Patients (n = 17)	p-value
WBC	7.0 [5.6, 8.2]	7.4 [6.2, 8.2]	6.9 [5.3, 8.4]	7.7 [4.9, 13.0]	0.72
Hemoglobin	12.6 [11.9, 13.3]	13.1 [12.4, 13.9]	14.0 [12.5, 14.3]	9.9 [9.3, 11.1]	<0.001
Platelets	288 [248, 353]	273 [218, 308]	293 [243, 316]	200 [148, 259]	0.004
ESR	10 [6, 20]	6 [2, 10]	8 [5, 10]	50 [27, 67]	<0.001
CRP	1.40 [0.12, 5.20]	0.18 [0.06, 0.57]	0.42 [0.14, 1.56]	10.45 [3.80, 17.40]	<0.001
Procalcitonin	0 [0, 0]	0 [0, 0]	0 [0, 0]	6.68 [1.93, 21.58]	<0.001

Figure 1. ESR in JIA vs. Infection

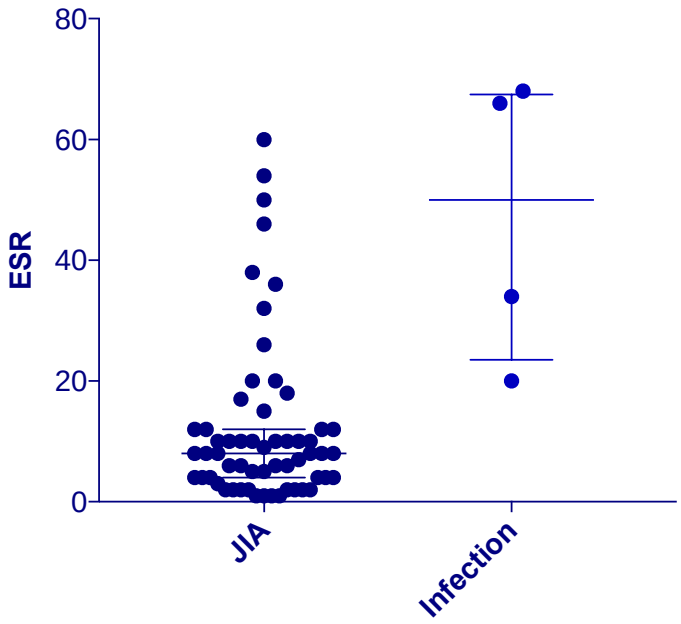

Figure 2. CRP in JIA vs. Infection

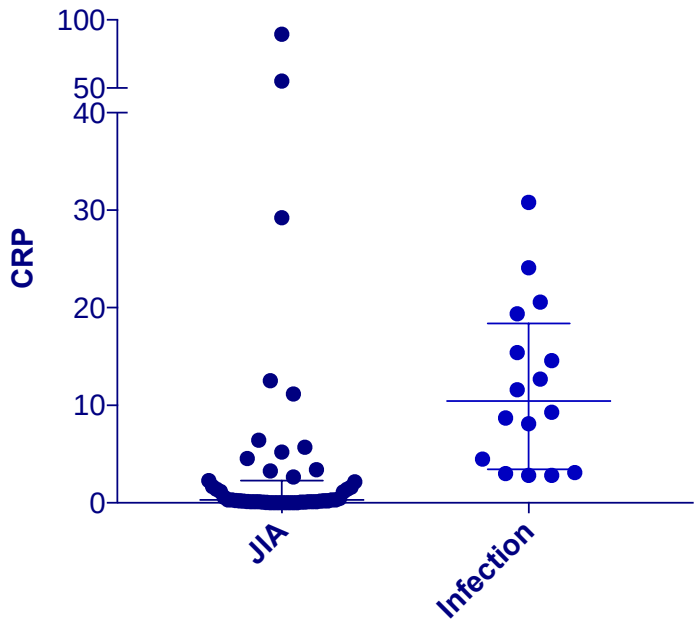

Figure 3. PCT in JIA vs. Infection

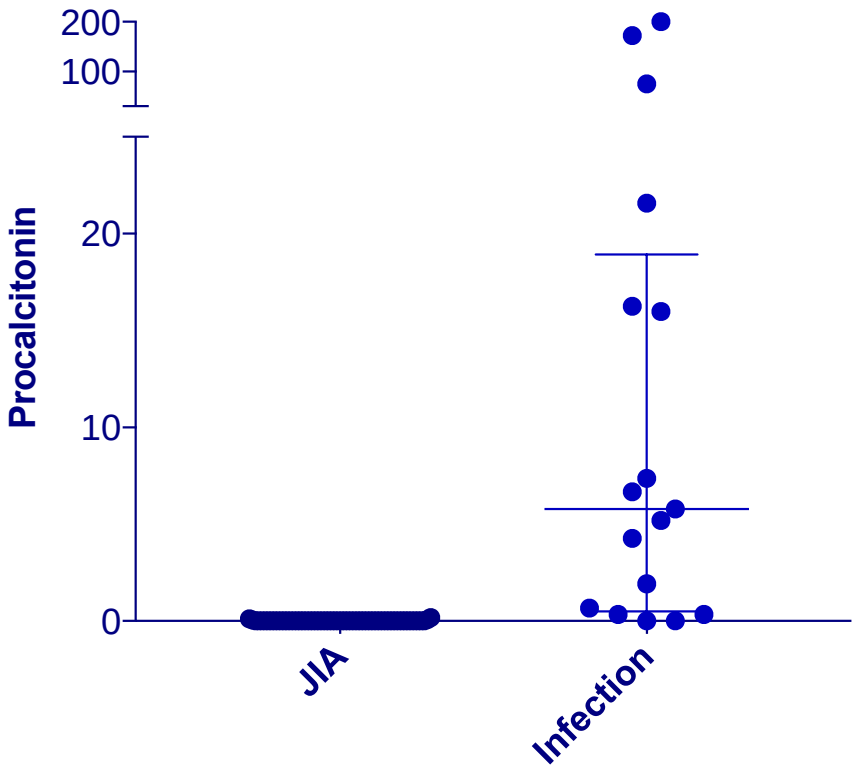

Table 4. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for PCT

	Point Estimate	Confidence Interval
Sensitivity	94.1%	71.3% - 99.9%
Specificity	98.3%	90.9% - 99.9%
Positive Predictive Value	94.1%	69.5% - 99.1%
Negative Predictive Value	98.3%	89.7% - 99.7%

DISCUSSION

To our knowledge, this is the first study to examine PCT specifically in children with JIA, for its utility in differentiating infection and non-infectious inflammatory disease activity. Korczowski et al evaluated procalcitonin, CRP, and ESR in 28 children with autoimmune disease, 9 of whom had juvenile arthritis.[15] They found that while ESR and CRP are sometimes elevated in children with autoimmune disease, PCT remains low in this population. This study concluded that PCT may be useful for differentiation of infection and inflammatory disease activity; however, findings were not disease specific.

Recently, multiple studies have been done evaluating PCT and additional biomarkers for differentiation of infection and inflammatory disease activity in systemic autoimmune diseases, especially systemic lupus erythematosus.[16,17] These studies have repeatedly shown that PCT, in conjunction with other biomarkers, can reliably differentiate infection from an inflammatory disease flare. A meta-analysis performed by Serio et al in 2014 confirmed this finding.[18]

Here, we evaluated PCT as a marker for infection vs. non-infectious inflammation in children with JIA specifically. Our study indicates that serum ESR, CRP, and PCT

levels are all biomarkers that can be used to distinguish serious bacterial infection from active JIA at presentation. However, PCT is the most accurate, with the least overlap between patients with infection and non-infectious inflammatory arthritis, and a high sensitivity and specificity. This finding can help clinicians direct therapy more accurately and swiftly at disease onset. However, PCT is not a useful biomarker to assess disease activity in JIA, as PCT levels did not differ between patients with active incident JIA and quiescent prevalent JIA.

Some strengths of this study include recruitment of multiple groups of patients for comparison, including children with active incident JIA, quiescent prevalent JIA, healthy pre-surgical candidates, and children with serious bacterial infection. Some limitations of our study are that this was performed at a single center with a limited sociodemographic population. It is important to note that the age and race differed between the group of patients with infection and the other three groups; however, there is currently no data to support that PCT differs by age or race.

This study is the first step towards establishing a biomarker panel that can differentiate infection and inflammatory disease activity in children with JIA. We have shown that in this population of patients, PCT remains reliably low, even when disease is active and other more commonly used inflammatory markers are elevated. Further studies are needed to assess additional biomarkers in conjunction with PCT for distinction of

infection and disease flare, throughout disease course. Further evaluation and measurement of serum PCT for differentiating JIA flares from less severe infections is also required.

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