

Serum procalcitonin for discrimination between septic and non-septic arthritis

T. Hügler¹, P. Schuetz²,
B. Mueller², G. Laifer³,
A. Tyndall¹, S. Regenass¹,
T. Daikeler¹

¹Department of Rheumatology,

²Department of Endocrinology Diabetes and Clinical Nutrition, ³Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Switzerland.

Thomas Hügler, MD; Philipp Schuetz, MD; Beat Mueller Professor; Gerd Laifer, MD; Alan Tyndall, Professor; Stephan Regenass, MD; Thomas Daikeler, MD.

Please address correspondence to:
Dr. Thomas Hügler, Department of Rheumatology, University of Basel, Felix-Platter-Spital, Burgfelderstrasse 101, CH-4012 Basel, Switzerland.
E-mail: hueglet@uhbs.ch

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ABSTRACT

Background. Early differentiation between septic and non-septic arthritis is difficult. A previous study showed promising diagnostic accuracy of serum Procalcitonin (PCT) in septic arthritis, limited by a low sensitive PCT test kit.

Objective. To investigate the diagnostic value of PCT in patients with septic and non-septic arthritis using a novel test with low detection limit.

Methods. Forty-two patients, 28 with non-septic and 14 with septic arthritis were prospectively included. For each patient, gram stain, culture and polarization microscopy of synovial fluid was done and PCT, C-reactive protein (CRP), white blood cell count, uric acid and blood cultures were taken. Patients with septic arthritis, patients with non-septic arthritis with and without concomitant infection were compared.

Results. Patients with septic arthritis had a significant higher PCT concentration than patients with non-septic arthritis ($p < 0.0001$). At a cut-off of 0.1 (0.25) ng/ml, sensitivity for septic arthritis was 100(93)% and specificity 46(75)%. Specificity rose to 93% after exclusion of patients with non-septic arthritis and concomitant infection. Both sensitivity and specificity for the diagnosis of septic arthritis were higher for PCT than CRP.

Conclusions. Our data suggest that PCT seems to be a highly sensitive and specific marker for septic arthritis, depending on the clinical setting. Further studies are warranted.

Introduction

Early differentiation between septic and non-septic arthritis and the possible decision for therapy remain a difficult task for the physician, because clinical signs and traditional markers of infection are of limited value (1, 2). Arthrocentesis with synovial gram stain and culture is considered as gold standard, however, the sensitivity of the gram stain is only 50-75% and culture is not available immediately (3). Serum procalcitonin (PCT) has emerged as a biomarker for the diagnosis of various bacterial infections and was found to have higher diagnostic accuracy as

compared to clinical characteristics or commonly used laboratory parameters, such as white blood cell count (WBC) and C-reactive protein (CRP) (4-7). In previous studies, the diagnostic accuracy of serum PCT has been analyzed in septic, crystal and rheumatoid arthritis with contradicting results (7-10). While serum PCT concentrations showed no significant difference in patients with bacterial and crystal arthritis in one study, another small study revealed significant difference with relatively low sensitivity and high specificity of PCT using a cut off of 0.5 ng/ml (8, 9). However, all studies were limited by a semi quantitative, low sensitive PCT assay with a functional detection limit of 0.3-0.5 ng/ml and a small and heterogeneous patient's cohort not excluding patients with concomitant infections.

The aim of this study therefore was to analyze the diagnostic accuracy of PCT in the differentiation of septic and non-septic arthritis using a PCT assay with higher analytical sensitivity and to compare PCT values with currently used routine clinical and microbiological diagnostic procedures. Furthermore, those patients with non-septic arthritis having a concomitant infection elsewhere were analyzed separately in order to account for PCT elevation by non-arthritis processes.

Patients and methods

The Institutional Review Board classified the study as a quality control study and waived the need for patient informed consent.

We prospectively included patients ≥ 16 years of age at our institution with mono- or oligoarthritis and patients, who developed arthritis while being already hospitalized for reasons other than arthritis. Patients with antibiotic treatment or surgery within the last 5 days were excluded. All patients had a diagnostic and therapeutic work up including arthrocentesis, culture and gram-stain as well as polarization microscopy of synovial fluid, blood culture collection, radiography of the involved joint and of the thorax, and urinary analysis. Laboratory analysis included the determination of white blood cell count, CRP, PCT and uric

Conflict of interest: Drs. P. Schuetz and B. Mueller have served as consultants and have received payments from Brahms to attend meetings, for travel expenses, speaking engagements and research; Drs. Hügler, Laifer, Tyndall, Regenass and Daikeler have declared no competing interests.

acid from the routinely collected blood analysis of all patients.

Septic arthritis was defined by detection of bacteria in the synovial fluid by gram stain or culture or detection of bacteria in blood cultures in the presence of arthritis. Crystal arthropathy was defined by the finding of urate or calcium pyrophosphate crystals in the synovial fluid by polarization microscopy and absence of bacterial growth in culture of synovial fluid and blood. Rheumatoid arthritis was classified according to ACR criteria (11).

CRP concentrations were determined by an enzyme immunoassay having a detection limit of <5 mg/l (EMIT, Merck Diagnostica, Zurich, Switzerland). PCT was determined using an ultra-sensitive immuno-luminometric assay having a functional detection limit of <0.02 ng/ml (PCT sensitive LIA®, Brahms, Berlin, Germany).

Statistical analysis

To evaluate differences between groups, the unpaired Student's *t*-test for normally distributed continuous variables and the Mann-Whitney U test or Fisher's exact test for categorical variables were used, as appropriate. Diagnostic value of individual laboratory markers for diagnosing septic or non-septic arthritis were compared by receiver operating characteristic (ROC) analysis. The area under the ROC curve (AUC) was the measure of the accuracy of the laboratory parameter to distinguish two groups. A *p*-value <0.05 (for a 2-sided test) was considered statistically significant. All calculations were performed using statistical software MedCalc for Windows (version 7.2.1.0, Mariakerke, Belgium).

Results

Forty-two patients were included in this study. Baseline characteristics are presented in Table I. Underlying comorbidities were equally distributed in both groups. Three patients with septic and one patient with non-septic arthritis suffered from underlying rheumatoid arthritis.

Twenty-eight patients were classified as having non-septic arthritis and 14 as having septic arthritis. Non-septic

Table I. Baseline characteristics of all patients.

	Infectious arthritis (n = 14)	Non-infectious arthritis (n = 28)	<i>p</i> value
Gender (female/male)	9/5	14/14	
Mean Age (SD)	61.6 (20.1)	64.8 (17.1)	
Joints involved (<i>more than 1 joint was involved in 5 patients</i>)			
- toe	1	0	
- ankle	4	4	
- knee	4	18	
- hip	1	0	
- sternoclavicular	2	0	
- shoulder	3	3	
- elbow	1	1	
- wrist	1	3	
- finger	0	1	
- prosthetic joint	4	0	
Clinical presentation			
- fever	10 (71%)	5 (17%)	=0.05
- pain	11 (78%)	23 (82%)	>0.05
- swelling	10 (71%)	29 (92%)	>0.05
- redness	8 (57%)	22 (75%)	>0.05
Laboratory data			
leucocytes (x10 ⁹ /l)*	16 (16-16)	8.7 (6.3-12.8)	0.09
C-reactive protein (mg/l)*	167 (121-230)	88 (25-161)	0.007
procalcitonin (ng/ml)*	2.5 (2.3-2.6)	0.1 (0.07-0.35)	<0.0001

SD: standard deviation; *median (IQR, interquartile range)

arthritis included crystal arthropathy (16), undifferentiated arthritis (8), reactive arthritis (3) and rheumatoid arthritis (1). Concomitant infections were present in 13 out of the 28 patients with non-septic arthritis including urinary tract infection (5), pneumonia (4), cellulitis (2), esophageal candidiasis (1) and cholecystitis (1).

In septic arthritis, the isolated microorganisms were *Staphylococcus aureus* (n=7), *Streptococcus pyogenes* (n=1), *Streptococcus pneumoniae* (n=1), *Escherichia coli* (n=1), *Salmonella enteritidis* (n=1), *Streptococcus agalactiae* (n=1), *Listeria monocytogenes* (n=1) and *Propionibacterium acnes* (n=1). Growth of bacteria in blood cultures was detected in 6 out of 14 cases. Associated localized infections in patients with septic arthritis were detected in two cases (pneumonia and urinary tract infection). In one patient, septic arthritis occurred after intraarticular steroid injection and in another subsequent to proximal soft tissue infection.

There was no significant difference in the median WBC (x10⁹/L) in septic arthritis compared to non-septic arthritis (8.7 vs. 16) (*p*=0.09). Median CRP values (mg/l) (167 vs. 88 *p*=0.007) and

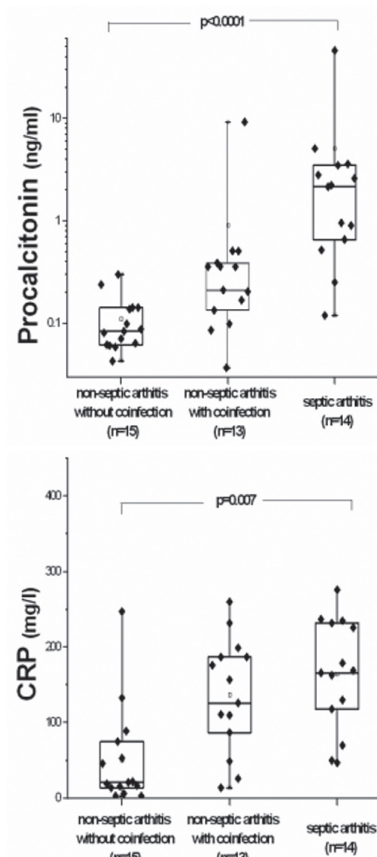
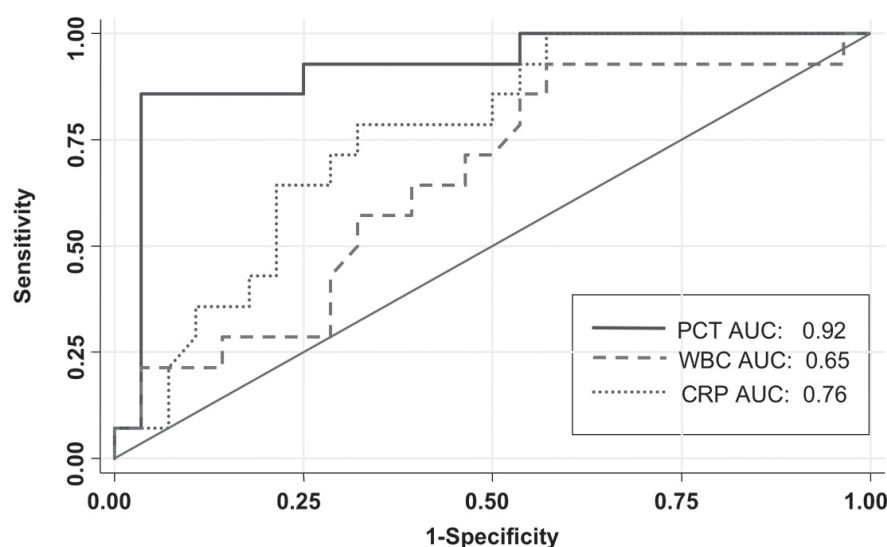


Fig. 1. Box-plot of PCT and CRP values in septic and non-septic arthritis with and without co-infection.

Table II. Sensitivity, specificity and negative predictive value (NPV) for PCT and CRP in septic and non-septic arthritis.

Cut-off	Septic vs. non-septic arthritis			Septic vs. non-septic arthritis without concomitant infection		
	Sensitivity %	Specificity %	NPV %	Sensitivity %	Specificity %	NPV %
PCT (ng/ml)						
0.1	100	46	100	100	60	100
0.25	93	75	95	93	93	94
CRP (mg/l)						
50	93	46	92	93	66	91
118	79	68	86	79	87	82

**Fig. 2.** Receiver operating characteristic (ROC) curves analysis for PCT, CRP and WBC in septic arthritis.

PCT (ng/ml) (2.5 vs. 0.1 $p < 0.0001$) values were significantly higher in the group with septic arthritis as compared to the patients with non-septic arthritis (Fig. 1). At an optimal cut off of 0.25 ng/ml, ROC analysis showed a sensitivity of 93% and a specificity of 75% of PCT for septic arthritis compared to a sensitivity of 79% and a specificity of 68% for CRP using a cut off of 118 mg/l. Sensitivity, specificity and negative predictive values of PCT and CRP for different cut off levels are indicated in Table II. The area under the curve (AUC) for PCT was 0.92 (95%CI 0.82-1.00) compared to 0.76 (95%CI 0.62-0.91) for CRP ($p = 0.03$) and 0.65 (95%CI 0.48-0.83) for WBC ($p = 0.003$) (Fig. 2). After exclusion of patients with non-septic arthritis suffering from concomitant infection, the specificity of PCT rose to 93% and that of CRP to 87%. Subsequently, the AUC was 0.97

(95%CI 0.92-1.00) for PCT and 0.87 (95%CI 0.74-1.00) for CRP ($p = 0.11$).

Discussion

This study demonstrates that PCT is a valid marker for early distinction between septic and non-septic arthritis. By using for the first time a highly sensitive PCT test kit in this study, the sensitivity for the diagnosis of septic arthritis could be raised compared to previous publications (8). We demonstrated that septic arthritis in patients with serum PCT values measured with a high sensitivity assay is highly unlikely if below 0.1 ng/ml and unlikely if below 0.25 ng/ml. Conversely, in arthritis without distant concomitant bacterial infection, serum PCT elevation over 0.25 ng/ml points towards the presence of septic arthritis. As compared to CRP and WBC count, PCT is more specific and more sensitive

for the diagnosis of septic arthritis as determined by the ROC curve analysis with an AUC significantly higher for PCT than for CRP or WBC in the overall analysis. After exclusion of patients with concomitant infections this difference did not reach statistical significance. This is most likely due to the low patient number in the sub-group. The low number of patients included and the high incidence of co-infections in the non-septic arthritis group are thus the main limitations of the study. The latter is probably due to the more severe ill patients admitted to a university hospital and the inclusion of already hospitalized patients, having a higher rate of co-infections compared to patients attending an outpatient clinic. We showed that co-infection reduces specificity of PCT and CRP for the diagnosis of septic arthritis. Therefore we speculate that in an outpatient setting in daily practice the specificity of PCT for septic arthritis could be higher, because of less co-morbidity. The high sensitivity and specificity of the ultra sensitive PCT assay for septic arthritis should be confirmed in larger trials and may subsequently justify an intervention study with antibiotic therapy, guided by PCT levels.

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