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BRIEF REPORT

Is procalcitonin a marker of invasive bacterial infection in acute sickle-cell vaso-occlusive crisis?

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Abstract Fever is often present during painful vaso-occlusive crisis (VOC) in sickle-cell disease (SCD), but does not always indicate infection. The aim of our study was to test procalcitonin as a marker of invasive bacterial infection in VOC. Consecutive SCD adults hospitalized for VOC were included. Data were collected at admission and within 24 h after the onset of fever. We distinguished patients with clinically defined and microbiologically documented invasive bacterial infection from patients with no evidence of invasive bacterial infection and who fared well without antibiotics. One hundred and twelve patients were enrolled (61% females, median age 23 years, 88% homozygous SCD). All patients with procalcitonin (PCT) level $\geq$1 μg/L had an invasive bacterial infection, but two patients (33%) with an invasive bacterial infection had a PCT level <1 μg/L. High levels of PCT indicate invasive bacterial infection. However, a single low PCT level without follow-up measurement cannot rule out an invasive bacterial infection and should not withhold the prescription of antibiotics.

Keywords Sickle-cell anemia · Fever · Infection · Procalcitonin

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Introduction

Painful vaso-occlusive crisis (VOC) is the most frequent acute complication in sickle-cell disease (SCD). Elements of the systemic inflammatory response syndrome (SIRS) are difficult to interpret during VOC, since fever is often present, tachycardia can be secondary to anemia and pain, and tachypnea is also the first sign of acute chest syndrome. Because of a relative asplenic state in SCD, the risk of severe infection, especially with encapsulated bacteria like *Streptococcus pneumoniae*, is high and antibiotics are frequently prescribed in case of fever. However, widespread use of antibiotics contributes to the development of bacterial resistance and exposes patients to side effects. To guide the use of antibiotics, it would be useful to have a marker that could distinguish invasive bacterial infections from viral infections or non-specific inflammation due to the VOC itself [1].

White blood cell count (WBC) and C-reactive protein (CRP) are often raised by the inflammatory reaction related to the vaso-occlusive phenomenon. Procalcitonin (PCT) is a protein of unclear cellular origin [2] that has been used to differentiate invasive bacterial and fungal infections from viral and non-infectious causes of SIRS in other settings. In adults, its usefulness has been shown in acute respiratory distress syndrome [3], meningitis [4], necrotizing pancreatitis [5], and after organ transplantation [6], whereas other

markers of inflammation such as CRP or WBC were not discriminative.

In the present study, we wanted to evaluate PCT as a marker of invasive bacterial infection during VOC in patients with SCD. According to the architecture of diagnosis research proposed by Sackett and Haynes [7], this study is designed to answer a phase I question: Does the level of PCT increase across prespecified groups with increasing frequency of invasive bacterial infection?

Patients and methods

Included patients

This prospective monocentric non-interventional study was performed in the referral center for adult SCD of a university hospital, in accordance with national ethics laws. It included consecutive patients admitted to the internal medicine department for VOC between May 1, 2007 and July 15, 2008. All patients had major sickle-cell syndrome (SS, SC, or Sβ-thalassemia) confirmed by hemoglobin or DNA analyses and were either Africans or West Indians. VOC is defined as an acute painful episode, mostly in the bones, due to the sickling of red blood cells in the capillaries, resulting in an inflammatory reaction, ischemia, intense pain, and necrosis. Acute chest syndrome is defined as acute thoracic manifestations (chest pain, cough, dyspnea, expectorations, lung auscultation abnormalities) and a new chest infiltrate on roentgenogram. Fever was defined as body temperature over 38°C measured with a tympanic thermometer.

Since PCT levels decrease quickly in patients receiving antibiotics [8], we excluded all patients on antibiotics at admission. The influence of the human immunodeficiency virus and active B or C hepatitis on PCT levels is unknown, but no SCD patient suffering from these infections was admitted during the study period.

Recorded data

The following data were collected within 24 h of admission: age, sex, disease type (SS, SC, Sβ-thalassemia), temperature, blood pressure (BP), heart rate, WBC, hemoglobin, plasma fibrinogen, CRP, lactate dehydrogenase (LDH), and PCT levels. PCT was measured in plasma lithium heparin samples using TRACE-Technology (Kryptor, BRAHMS, France). The threshold of detection of PCT was 0.03 ng/mL.

If fever occurred during hospitalization, clinical signs of infection were again recorded at that time; blood samples were drawn for WBC, hemoglobin, plasma fibrinogen, CRP, LDH, and PCT levels; bacterial cultures were performed on blood and urine in all febrile patients, and on other oriented samples if necessary. In case of acute chest syndrome, urinary pneumococcal and *Legionella* antigen tests were also performed.

Categorization of patients

Four weeks after discharge, a synthesis of each case was made, and patients were categorized into four groups with increasing frequency of invasive bacterial infection, with regard to their clinical evolution and their laboratory and imaging results:

- Group 1: VOC without fever, without acute chest syndrome, and with no evidence of invasive bacterial infection.
- Group 2: VOC with fever but without clinical or radiological evidence of invasive infection, and with negative bacterial cultures and other microbiologic tests.
- Group 3: acute chest syndrome.
- Group 4: febrile VOC with documented invasive bacterial infection (except pneumonia).

Documented invasive bacterial infections were defined by SIRS and clinical or radiological findings related to the origin of the infection, confirmed by microbiological cultures. Antibiotics were prescribed according to usual practice for suspected or confirmed bacterial infection, and were routinely prescribed for acute chest syndrome. For local infections, as long as there was no fever, the decision of administrating antibiotics was based on the clinical picture and elements of the patient's past medical history, such as recurrent episodes of severe infections. Patients with local infections and no fever were classified in group 1.

If a patient was admitted several times during the study period and was categorized in the same group, we only took the data from the first hospitalization (11 patients).

Statistical methods

This is a pilot study for which no data is available to calculate precisely the required sample size. The sample size was, therefore, determined by feasibility, as recommended for phase I studies [9].

We analyzed data recorded at admission for patients who did not have fever during their hospitalization, and data recorded within 24 h after the onset of fever for those who did. Quantitative variables were summarized as median [interquartile range] and categorical data as number (percentage). We used Cuzick's test for quantitative variables and the Cochrane–Armitage test for categorical variables to look for a trend across the four groups with

increasing probability of bacterial infection. Then, we excluded patients who received antibiotics for local infection or suspected but undocumented invasive infection, because invasive bacterial infection could be neither proved nor disproved. We only considered patients from groups 1, 2, and 3 who fared well without antibiotics, since they were certainly free of invasive bacterial infection (53 patients). We compared their values of PCT, CRP, and WBC to those of patients with a documented bacterial infection (group 4) using the Mann–Whitney test. For all tests, *P*-values <0.05 were considered to be statistically significant.

Results

Description of the study population

The study included 112 cases admitted for VOC. Sixty-eight (61%) were women, and the median age was 23 years [21–28]. Ninety-nine (88%) had homozygous (SS) sickle-cell disease, four (4%) had heterozygous SC sickle-cell disease, and nine (8%) had Sβ-thalassemia. Fifty-two (46%) cases were in group 1 (no fever and no evidence of invasive bacterial infection), 16 (14%) were in group 2 (fever but no other evidence of invasive bacterial infection), 37 (33%) were in group 3 (acute chest syndrome), and seven (6%) were in group 4 (documented invasive bacterial infection). Documented invasive bacterial infections involved the upper urinary tract in five cases, all with *Escherichia coli* susceptible to all of the tested antibiotics, and two septicemias from central venous catheters, one with *Klebsiella oxytoca* and *Citrobacter freundii*, and the other with methicillin-sensitive *Staphylococcus aureus*. Ten cases of non-invasive bacterial infections were classified in group 1: three cases of lower urinary tract infections with *E. coli* susceptible to all of the tested antibiotics, one case of infection around chronic leg ulcers with *Pseudomonas aeruginosa* and methicillin-sensitive *S. aureus*, one case of dental infection, and five cases of upper respiratory tract infection without microbiological documentation.

Characteristics of the study groups

There was no age or sex difference across the groups. As expected, there was a trend toward higher temperature, higher heart rate, and longer hospital stay from group 1 (no fever) to group 4 (documented invasive bacterial infection). There was no such trend for age, sex, SCD type, blood pressure, and hemoglobin (Table 1).

Antibiotics were given to all patients with a documented invasive bacterial infection. They were administered to half of the febrile patients without definite evidence of bacterial infection (group 2) because of high, protracted, and poorly tolerated fever, mostly in fear of pneumococcal infection. Thirty-four (92%) patients with an acute chest syndrome received antibiotics, in line with usual practice (antibiotics

Table 1 Clinical and biological variables in the study population

	Group 1 ($N = 52$)	Group 2 ($N = 16$)	Group 3 ($N = 37$)	Group 4 ($N = 7$)	*P*-value
Age (years)	22 [20.5–27.5]	22 [20–30]	25 [22–28]	20 [18–25]	0.73
Females	39 (75%)	6 (38%)	17 (46%)	6 (86%)	0.07
Genotype (SS/SC/Sβ0/Sβ+)	47/1/1/3	13/1/0/2	33/2/0/2	6/0/0/1	0.72
Temperature (°C)	37 [36.8–37.1]	38.6 [38.2–39.2]	38.2 [37.5–39.0]	38.8 [38.1–39.9]	<0.001
Systolic BP (mmHg)	114 [110–121]	118 [111–135]	116 [110–128]	109 [108–110]	0.47
Diastolic BP (mmHg)	66 [59–70]	70 [60–78]	70 [60–73]	60 [54–61]	0.63
Heart rate (bpm)	79 [70–87]	87 [80–100]	85 [76–101]	90 [67–103]	0.003
PCT (μg/l)	0.13 [0.08–0.18]	0.29 [0.14–0.6]	0.25 [0.15–0.8]	1.98 [0.10–5.99]	<0.001
CRP (mg/l)	21 [6–58]	119 [75–171]	102 [37–179]	123 [36–184]	<0.001
WBC (G/l)	10.9 [8.2–13.9]	13.1 [10.3–15.2]	13.9 [10.5–16.8]	19.5 [11.1–26.5]	<0.001
LDH (IU/l)	370 [291–478]	547 [398–935]	503 [336–731]	484 [348–544]	0.02
Fibrinogen (g/l)	4.0 [3.2–4.8]	4.3 [4.0–5.9]	4.9 [3.4–6.1]	6.9 [5.7–7.8]	0.008
Hemoglobin (g/dl)	8.3 [7.3–9.2]	8.5 [7.6–9.6]	7.9 [6.9–9.2]	7.1 [6.3–8]	0.12
Length of stay (days)	6 [4–8]	8 [7–11]	9 [8–11]	8 [7–14]	<0.001
Antibiotics	10 (19%)	8 (50%)	34 (92%)	7 (100%)	<0.001

Group 1 no fever; group 2 fever but no other evidence of invasive bacterial infection; group 3 acute chest syndrome; group 4 documented invasive bacterial infection (except pneumonia). Comparisons between groups were performed with Cuzick's test for trend (quantitative variables) or the Cochrane–Armitage test for trend (categorical variables)

BP blood pressure, *bpm* beats per minute, *PCT* procalcitonin, *CRP* C-reactive protein, *WBC* white blood cell count, *LDH* lactic dehydrogenase

were not prescribed in three patients because of mild respiratory symptoms, no fever, and fast recovery after chest physiotherapy and pain control). Ten (19%) patients without fever (group 1) received antibiotics because of local infections considered as a potential trigger of the VOC.

Diagnostic value of PCT, CRP, and WBC

PCT, CRP, and WBC all showed a highly significant trend toward higher values from group 1 (no fever) to group 4 (documented bacterial infection) (Table 1). Figure 1 shows the distribution of PCT, CRP, and WBC values in patients with documented bacterial invasive infection (group 4) and in patients from the other groups who were very unlikely to have an invasive bacterial infection, since they fared well without antibiotics. Table 2 shows the diagnostic accuracy of PCT, CRP, and WBC to distinguish patients with a documented bacterial infection from patients who recovered without antibiotics (free from invasive bacterial infection). All patients with a documented invasive bacterial infection had WBC ≥10 G/L; nevertheless, 27 (51%) patients who had a good outcome without antibiotics, thus considered to have no invasive bacterial infection, also had WBC ≥10 G/L. All patients with PCT level ≥1 μg/L had an invasive bacterial infection; nevertheless, two (33%) patients with an invasive bacterial infection had a PCT level <1 μg/L (0.09 and 0.10 μg/L, respectively). The first patient had an infection from a central venous catheter, with low fever, positive blood cultures from the central line with methicillin-sensitive *S. aureus*, and negative peripheral blood cultures. The second patient had diffuse bone pain at admission, flank pain, fever, and a confirmed urinary tract infection with positive urine cultures with *E. coli* diagnosed 2 days later. The CRP level was ≥10 mg/L in five patients (83%) with invasive bacterial infection and was unavailable in one; nevertheless, 33 patients (70%) with no evidence of invasive bacterial infection also had a CRP level ≥10 mg/L.

Discussion

Our results suggest that PCT levels ≥1 μg/L are indicative of invasive bacterial infection. On the contrary, a single low PCT level without follow-up measurement cannot rule out an invasive bacterial infection in a sick patient and should not be used to withhold antibiotics, since two patients with invasive bacterial infection had very low PCT levels. The microorganisms involved in these two cases are not known to cause low-level inflammation that could explain the low level of PCT.

The lack of a gold standard for invasive bacterial infection was a major limitation of our study.

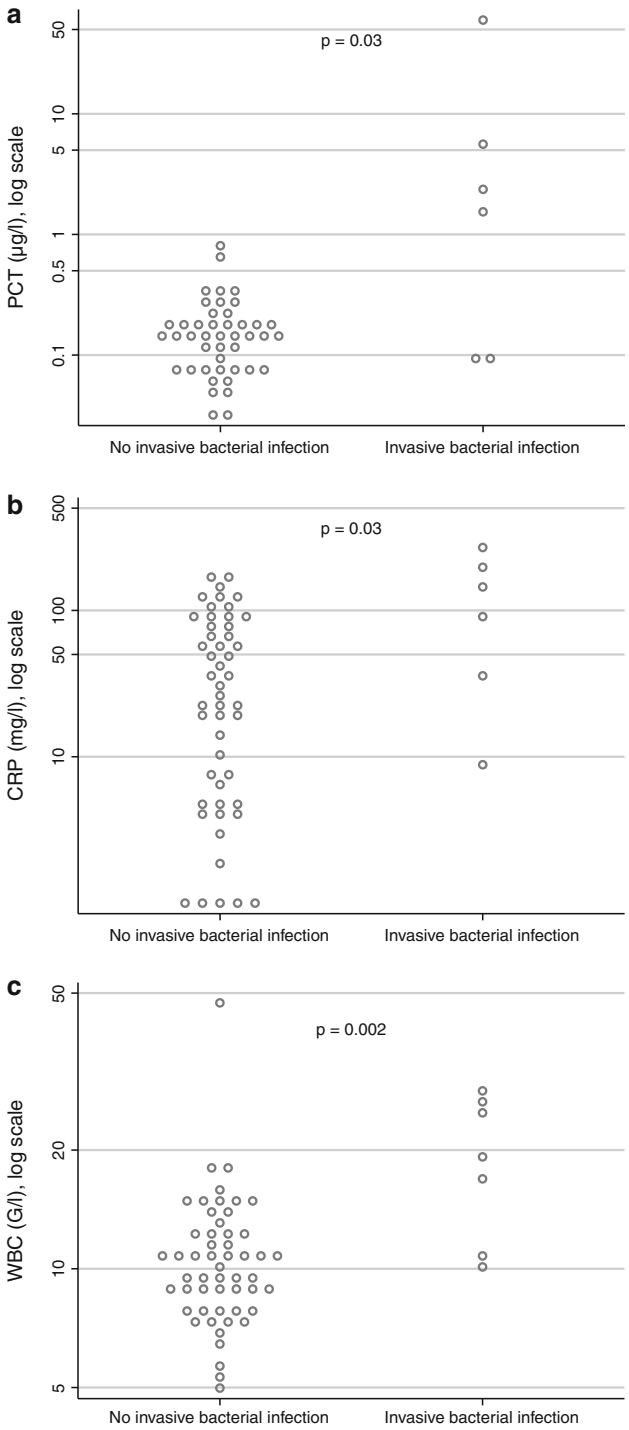

Fig. 1 Distribution of procalcitonin (**a**), C-reactive protein (**b**), and white blood cell count (**c**) in patients with documented invasive bacterial infection and patients without invasive bacterial invasion (patients who fared well without antibiotics). *PCT* procalcitonin; *CRP* C-reactive protein; *WBC* white blood cell count

Microbiological cultures are insensitive. One pair of blood cultures was performed in all febrile patients—two or three pairs in most of them—and other microbiological cultures if clinically indicated. No diagnostic blood culture was

Table 2 Diagnostic value of procalcitonin, C-reactive protein, and white blood cell count to distinguish patients with documented invasive bacterial infection from patients without invasive bacterial invasion (patients who fared well without antibiotics)

	Area under the ROC curve [95% CI]	Positive test	Sensitivity [95% CI]	Specificity [95% CI]	Negative predictive value [95% CI]	Positive predictive value [95% CI]
Procalcitonin	0.77 [0.47, 1.00]	≥1 μg/l	67% [22, 96]	100% [92, 100]	96% [85, 100]	100% [40, 100]
C-reactive protein	0.77 [0.54, 1.00]	≥10 mg/l	83% [36, 100]	32% [20, 47]	94% [71, 100]	13% [4, 27]
White blood cell count	0.86 [0.70, 1.00]	≥10 G/l	100% [59, 100]	49% [35, 63]	100% [87, 100]	21% [9, 38]

ROC receiver operating characteristic, *CI* confidence interval

performed in afebrile patients. The diagnosis of invasive bacterial infection was reached in patients with positive microbiological cultures, along with clinical signs of invasive bacterial invasion, including fever. On the other hand, invasive bacterial infection was excluded in patients who had negative microbiological cultures and recovered from their VOC without antibiotics. Patients with localized infection were classified in group 1, since they had no fever, and since previous works have shown that PCT does not rise in localized infections [10]. Patients with chest syndrome were classified in a specific group, since almost all of them receive antibiotics regardless of bacterial documentation to prevent a severe pneumococcal infection. Due to a low incidence of documented invasive bacterial infections in our department (seven cases in 16 months), we decided to stop the study. However, the finding of patients with documented infections and very low PCT levels already shows that normal PCT levels are insufficient to withhold antibiotics in patients with VOC and fever. Although it may add diagnostic information, the evolution of the PCT level 24 h after the first measurement of PCT was not analyzable because of the many missing values, mostly due to the difficulty in obtaining daily blood samples from painful sickle-cell patients.

We found only one publication describing the usefulness of PCT in sickle-cell disease [11]. The authors of this study concluded that a PCT level ≤2 μg/L excludes serious bacterial infection in SCD patients with VOC, but our data rebut this statement. However, the comparison between studies is difficult because this study used a much less sensitive PCT assay.

Conclusion

Our study suggests that no single routine clinical or biological variable can definitively differentiate fever due to an invasive bacterial infection from fever secondary to the acute vaso-occlusive process in sickle-celldisease (SCD) acute painful vaso-occlusive crisis (VOC). High values of procalcitonin (PCT) seem to indicate invasive bacterial infection, but a single low PCT level without follow-up measurement values cannot be used to rule it out and withhold antibiotics in patients with VOC and fever.

Conflict of interest All authors declare no conflict of interest. This work received no financial support.

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