Original article
https://doi.org/10.18019/1028-4427-2025-31-2-218-225

Dependence of serum procalcitonin level on microflora in the infection site in chronic osteomyelitis

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Abstract

Introduction The study of procalcitonin (PCT) levels simultaneously with blood cultures for sterility is an important addition to the diagnostic algorithm for chronic osteomyelitis detection.

Purpose of work is to study the relationship of serum PCT with the microflora isolated from blood, wounds and fistulas in patients with chronic osteomyelitis.

Materials and methods A retrospective analysis of wound microflora, blood cultures for sterility, and procalcitonin test results was performed.

Results Gram-positive microorganisms prevailed in the microbial tests from wounds, fistulas and blood in patients with PCT less than 0.5 ng/ml and from 0.5 to 2.0 ng/ml. In patients with PCT levels from 2.0–10.0 and above10 ng/ml, both gram-positive and gram-negative bacteria were isolated. Among positive blood cultures, S. *epidermidis* strains were the most frequently isolated, followed by S. *aureus*, K. *pneumoniae*, S. *agalactae*, and S. *hominis* isolates. PCT in the blood of seven patients was higher than 10 ng/ml; and six patients had it from 2.0–10.0 ng/ml. Two subjects had a low PCT level, but an infectious agent was detected in their blood.

Discussion In patients with PCT lower than 0.5 ng/ml, gram-positive microorganisms are most often found in the microflora of wounds and fistulas. The proportion of patients with PCT values ⩾ 2 ng/ml and gram-negative bacteria in the focus was higher compared to patients with gram-positive microflora. Nevertheless, the detected high correlation relationship between the microbiocenosis of patients' wounds and procalcitonin values confirms the leading role of gram-positive bacteria in the development of osteomyelitis.

Conclusion In positive blood cultures, the serum PCT level was usually higher than 2.0 ng/ml. The presence of gram-negative bacteria in the blood, as well as in the wound, was accompanied by PCT values higher than 10 ng/ml.

Keywords: chronic osteomyelitis, procalcitonin, microflora, resistance

For citation: Shipitsyna IV, Osipova EV, Shastov AL. Dependence of serum procalcitonin level on microflora in the infection site in chronic osteomyelitis. *Genij Ortopedii*. 2025;31(2):218-225. doi: 10.18019/1028-4427-2025-31-2-218-225.

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INTRODUCTION

Chronic osteomyelitis is a complex and difficult to treat bacterial or fungal bone infection characterized by progressive inflammatory destruction, necrosis and proliferation in the area of bone damage that develop due to complications of the wound process if it communicates with the bone, surgical interventions or bacteremia [1–3]. As a rule, osteomyelitis is of exogenous origin, caused by microbial invasion, often with the formation of a biofilm [4–8]. Treatment of chronic osteomyelitis requires long-term and intensive antimicrobial therapy, which leads to the risk of resistance. Moreover, osteomyelitis is dangerous due to complications (sepsis, bacteremia, etc.).

In recent years, there has been renewed interest in studying the role of various biomarkers (C-reactive protein, interleukins 6 and 8, lactate, presepsin, procalcitonin, and others) in the diagnosis and risk assessment of inflammatory syndromes [9–11]. Among them, procalcitonin (PCT) stands out and is considered a specific marker of bacterial infection [12–16]. It is known that PCT levels in the blood serum of healthy people are lower than 0.1 ng/ml. In severe bacterial and generalized fungal infections, PCT concentration quickly grows, but remains low in viral infections and nonspecific inflammatory diseases [17].

An isolated test for PCT is not informative enough, since its level can be elevated not only in acute and chronic infectious processes, including osteomyelitis, but also in various non-infectious conditions, such as autoimmune diseases, major surgeries, injuries, burns, prolonged cardiogenic shock, stress [12, 13, 18].

A positive blood culture is considered the gold standard for diagnosing bacteremia; however, negative results do not always rule out its absence [14, 19, 20]. Microbiological blood testing takes time, which does not allow its use as a rapid test [21]. High PCT values with negative blood culture results may indicate the presence of local inflammation, while elevated levels and a positive culture result confirm a systemic infectious process.

There are only a few studies devoted to the study of PCT levels and blood culture results for sterility in patients with chronic osteomyelitis. According to the literature, PCT plays the role of a sensitive and specific marker in the diagnosis of bone and joint infections [22]. Positive blood culture results were detected in 53 % of patients with vertebral osteomyelitis, 19 % with bone infection, and 7 % with paraimplant infection [7].

Diagnosis of osteomyelitis is established with a combination of clinical signs and symptoms, instrumental and laboratory studies, including analysis of microflora with determination of sensitivity to antibiotics [23]. A study of serum PCT simultaneously with blood cultures for sterility can provide additional information to physicians that would allow them to predict the course and outcome of the disease in patients with chronic osteomyelitis.

The **purpose** of work was to study the relationship of serum PCT with the microflora isolated from blood, wounds and fistulas in patients with chronic osteomyelitis.

MATERIALS AND METHODS

The study included patients (n = 123) with chronic osteomyelitis, regardless of its location and mechanism of occurrence, who were treated at the Purulent Osteology Clinic of the Ilizarov National Medical Research Center of Traumatology and Orthopaedics in the period from 2021 to 2023. The average age of patients was 55 years (IQR 43–66) and 70.3 % (71/101) were males. There were no significant differences in age between the groups of males and females (p = 0.32).

A retrospective analysis of microbiological cultures ($n = 294$), including blood for sterility, was performed. The procalcitonin test was performed simultaneously with blood sampling for sterility and on the third day after surgery. In case of unsatisfactory results, the test was repeated on days 5 to 9 as prescribed by the physician.

For rapid cultivation of pathogenic microorganisms in blood, an automatic analyzer of the Juno® Labstar 100 series was used. Microbial cultures were identified to the species level on a BactoScreen bacteriological analyzer (NPF Litekh); determination of the sensitivity of bacteria to antibacterial drugs by the disk diffusion method on the Mueller-Hinton medium. Depending on the type of microorganism, various sets of antibiotics were used:

— for non-fermenting gram-negative bacteria: 1 — tetracycline (30 mcg), 2 — amikacin (30 mcg), 3 — gentamicin (10 mcg), 4 — tobramycin (10 mcg), 5 — ciprofloxacin (5 mcg), 6 — levofloxacin (5 mcg), 8 — meropenem (10 mcg), 9 — imipenem (10 mcg), 15 — piperacillin/tazobactam (30/60 mcg), 23 — cefepime (30 mcg);

— for enterobacteria: 1 — tetracycline (30 μg), 2 — amikacin (30 μg), 3 — gentamicin (10 μg), 5 — ciprofloxacin (5 μg), 6 — levofloxacin (5 μg), 8 — meropenem (10 μg), 9 — imipenem (10 μg), 13 — ceftazidime (10 μg), 14 — cefotaxime (5 μg), 15 — piperacillin/tazobactam (30/60 μg);

— for staphylococci: 1 — tetracycline (30 mcg), 3 — gentamicin (10 mcg), 5 — ciprofloxacin (5 mcg), 10 — vancomycin (5 mcg), 12 — cefoxitin (30 mcg), 16 — clindamycin (2 mcg), 17 — erythromycin (15 mcg), 18 — fusidine (10 mcg), 19 — linezolid (10 mcg); 21 — rifampicin (5 mcg);

— for enterococci: 3 — gentamicin (30 mcg), 10 — vancomycin (5 mcg), 11 — ampicillin (2 mcg), 27 — norfloxacin (10 mcg), 19 — linezolid (10 mcg);

— for streptococci: 11 — ampicillin (2 mcg); 14 — cefotaxime (5 μg), 16 — clindamycin (2 μg), and 20 — benzylpenicillin (1 μg).

The results were assessed using the EUCAST criteria (European Committee on Antimicrobial Susceptibility Testing, Version 9.0, valid from 2019–01–01). Moderately resistant strains were classified as resistant.

The concentration of PCT in the blood serum was determined by a semi-quantitative method using the ICA-procalcitonin test (Russia). The results were interpreted in accordance with the manufacturer's recommendations:

< 0.5 ng/mL — systemic infection is unlikely, although localized infection is possible;

0.5 – < 2 ng/mL — systemic infection is possible, but other conditions (major trauma, recent surgery, severe cardiogenic shock) can also cause significant increases in PCT;

2 – < 10 ng/mL — systemic infection is likely;

⩾ 10 ng/mL — severe bacterial sepsis or septic shock is highly likely.

The results of the study are divided into two groups: positive and negative. Positive results, depending on the isolated microorganisms in the blood culture or focus, are divided into two subcategories: gram-positive and gram-negative bacteria.

The Gnumeric 1.12.17 software program was used for processing and statistical analysis of the obtained results. Quantitative variables are presented as median and interquartile range (IQR), and qualitative variables are presented as percentages. The nonparametric Wilcoxon test was used to determine differences between the groups. To study the relationship between procalcitonin values and the species composition of bacteria isolated from wounds, the Spearman rank correlation coefficient was calculated. The obtained data were interpreted using the Chaddock scale. Differences were considered significant at $p < 0.05$.

The clinical study was approved by the Ethics Committee of the Ilizarov National Medical Research Center of Traumatology and Orthopedics; it was conducted in accordance with the ethical standards of the Declaration of Helsinki.

RESULTS

Blood PCT concentrations lower than 0.5 ng/ml were observed in 52.0 % of the examined patients, from 0.5 to 2.0 ng/ml — in 19.5 % ($p = 0.13$), from 2.0–10.0 ng/ml — in 12.3 % ($p = 0.049$), and more than 10 ng/ml — in 16.2 % ($p = 0.049$). Gram-negative microflora in the blood was detected only in patients with PCT values greater than 10 ng/ml (Table 1).

Table 1

Number of patients with chronic osteomyelitis in dependence on PCT level

PCT, ng/ml	Количество пациентов по годам								Positive blood sterility test in the period from 2021 to 2023
	2021 ($n = 35$)		2022 ($n = 31$)		2023 ($n = 57$)		2021–2023 ($n = 123$)		
	n	%	*n*	%	*n*	%	*n*	%	
< 0.5	11	31.4	16	51.5	37	64.9	64	52.0	S. *epidermidis* ($n = 3$)
0.5–2.0	12	34.2	6	19.4	6	10.5	24	19.5* $p = 0.13$	S. *aureus* ($n = 1$), S. *hominis* ($n = 1$)
2.0–10.0	4	11.5	4	12.8	7	12.3	15	12.3* $p = 0.049$	S. *aureus* ($n = 3$), S. *pidermidis* ($n = 3$), *Streptococcus* spp. ($n = 2$)
⩾ 10.0	8	22.9	5	16.3	7	12.3	20	16.2* $p = 0.049$	S. *pneumoniae* ($n = 3$), S. *epidermidis* ($n = 2$)

Note: * — level of significance of differences between the number of examined patients with PCT values lower than 0.5 ng/ml

In the microbial landscape from the pathological focus in patients with PCT lower than 0.5 ng/ml and in the range 0.5–2.0 ng/ml, gram-positive microorganisms prevailed (Table 2). In patients with PCT from 2.0–10.0 ng/ml and above 10 ng/ml, both gram-positive and gram-negative bacteria were isolated. Among gram-negative bacteria from wounds and sinuses, enterobacteria were most often isolated, mainly strains of K. *pneumoniae*, and among gram-positive bacteria, strains of S. *aureus*. In five patients, there was no growth of microorganisms in the focus, while the PCT level was 0.5–2.0 ng/ml ($n = 4$), 2.0–10.0 ng/ml ($n =$). In one patient, bacteriological examination of wound culture did not reveal growth of pathogenic bacteria, but the test for blood sterility revealed the pathogen *Streptococcus* spp., while PCT was in the range of 2.0 to 10.0 ng/ml. In 10 patients, the microflora of wounds and fistulas did not match the results of blood cultures for sterility. The proportion of patients with PCT values ⩾ 2 ng/ml and gram-negative bacteria in the lesion was higher compared to patients with gram-positive microflora.

The correlation coefficients between the microbiocenosis of patients' wounds and the procalcitonin values indicate an inverse relationship between the studied features. The closeness of these relations was noticeable ($r = –0.57$ for gram-negative microflora) and high ($r = –0.74$ for gram-positive microflora) according to the Chaddock scale.

A positive blood sterility test was obtained in 17 patients. In two patients, K. pneumoniae strains were isolated during the initial blood test, with serum PCT values exceeding 10 ng/ml (Table 3). A repeated blood test showed a change in microflora to gram-positive with a simultaneous decrease in PCT to 0.5 ng/ml (patients No 1 and No 2, Table 3).

Table 2

Frequency of bacterial occurrence based on PCT values

Microorganism	PCT, ng/ml			
	0.5	0.5–2.0	2.0–10.0	More than 10
NFGNB	11	5	4	4
Enterobactereaceae	25	10	5	17
Total:	**36 (44.4 %)**	**15 (18.5 %)**	**9 (11.1 %)**	**21 (25.9 %)**
S. *aureus*	35	11	4	10
CoNS	15	6	2	7
Enterococcus sp.	8	2	–	5
Streptococcus sp.	1	1	–	1
Corynebacterium sp.	2	1	1	–
Total:	**61 (55.5 %)**	**21 (19.1 %)**	**7 (6. 4 %)**	**21 (19.1 %)**
No growth:	9	4	1	0

Note: NFGNB — non-fermenting gram-negative bacteria; CoNS — coagulase negative bacteria

Table 3

Active antibacterial drugs against bacteria isolated simultaneously from blood and wounds

No*	Blood microflora	Effective antibiotics	Microflora of wound and fistula	Effective antibiotics	PCT, ng/ml
1	K. *pneumoniae*	1	K. *pneumoniae*	1	> 10.0
	S. *epidermidis (MRSE)*	10	S. *epidermidis (MRSE)*	10	< 0.5
2	K. *pneumoniae*	2, 3	K. *pneumoniae*	2, 3	> 10.0
	S. *aureus*	All tested	S. *aureus*	All tested	< 0.5
3	K. *pneumoniae*	1	K. *pneumoniae*	1	> 10.0
			E. *faecalis*	1, 21	
4	K. *pneumoniae*	1–3, 6, 8, 9, 15, 22	E. *cloacae*	2, 9	> 10.0
			E. *faecalis*	7	
5	S. *epidermidis (MRSE)*	3,10, 16–18, 21	E. *coli*	2–6, 8, 9, 15, 22	< 0.5
			S. *aureus*	All tested	
6	S. *epidermidis (MRSE)*	10, 18, 19, 21	S. *epidermidis (MRSE)*	10, 18,19,21	2.0–10.0
7	S. *epidermidis (MRSE)*	1, 10, 18, 19, 21	S. *aureus (MRSA)*	1,10,18,19,21	> 10.0
8	S. *epidermidis*	All tested	S. *aureus*	All tested	2.0–10.0
9	S. *epidermidis*	All tested	P. *aeruginosa*	2, 3, 5, 8, 9, 15, 23	< 0.5
			A. *baumannii*	4, 8, 9, 15	
			S. *aureus*	All, but 16, 17	
10	S. *epidermidis (MRSE)*	1, 10, 18, 19, 21	S. *epidermidis (MRSE)*	1, 10, 18, 19, 21	2.0–10.0
			K. *pneumoniae*	2, 3, 8	
11	S. *epidermidis (MRSE)*	10, 18, 19, 21	E. *cloacae*	1–4, 6, 8, 23	> 10.0
12	S. *hominis (MRSH)*	10, 18, 19, 21	K. *pneumoniae*	1, 2, 3, 8	0.5–2.0
			P. *aeruginosa*	2, 3, 5, 8, 9, 15	
			E. *faecalis*	2, 10, 19	
13	S. *agalacteae*	All, but 1	No growth	–	2.0–10.0
14	S. *agalacteae*	11	E. *cloacae*	2, 6, 8, 9	> 10.0
			S. *epidermdis (MRSE)*	10, 19, 18, 21	
			E. *faecalis*	3, 10, 19	
15	S. *aureus*	All, but 5	P. *aeruginosa*	1, 3, 4	2.0–10.0
			A. *baumannii*	1, 4, 8, 9	
16	S. *aureus*	All tested	S. *aureus*	All tested	0.5–2.0
17	S. *aureus*	All tested	S. *aureus*	All tested	2.0–10.0

Note: * —numbers of patients with positive blood cultures. In the column with effective drugs, the antibiotics listed in the Materials and Methods section are marked with numbers.

Among positive blood cultures (*n* = 19), the most frequently isolated strains were S. *epidermidis* (*n* = 8, including 6 MRSE), followed by isolates of S. *aureus* (*n* = 4), K. *pneumoniae* (*n* = 4), S. *agalacteae* (*n* = 2), and methicillin-resistant S. *hominis* (*n* = 1).

Blood PCT was higher than 10 ng/ml in seven patients, and 2.0–10.0 ng/ml in six patients. Two patients had low PCT levels, and an infectious agent was detected in their blood. In six patients, the blood microflora and bacterial sensitivity to the tested antibacterial drugs coincided with the wound microflora. Gram-positive bacteria isolated from the blood were sensitive to most of the tested drugs. MRSE strains were isolated from the blood of six patients, two of whom had PCT above 10 ng/ml.

Bacterial strains belonging to the same taxon, isolated simultaneously from blood and wounds, were characterized by the same sensitivity to antibacterial drugs. Among the most effective antibacterial drugs against K. pneumoniae were tetracyclines and aminoglycosides, against bacteria of the genus *Staphylococcus* — glycopeptides, linezolid, rifampicin and fusidin.

In eight patients with PCT higher than 10 ng/mL, the value decreased to normal values within 7–9 days. In seven patients (in three of whom microorganisms were isolated from the blood), PCT did not decrease. In 13 of 15 patients with initial PCT values from 2.0 to 10.0 ng/mL, it decreased to normal values within 5–6 days.

DISCUSSION

According to the results of the study, gram-positive microorganisms, mostly S. aureus, were isolated from the focus in the patients with PCT less than 0.5 ng/ml. The rate of gram-negative bacteria was 1.7 times lower. At the same time, in patients with PCT values above 10 ng/ml, both gram-negative and gram-positive microorganisms were equally isolated from the lesion (wounds, sinuses, blood). Moreover, in all patients in who K. *pneumoniae* strains were isolated from the blood the PCT level was above 10 ng/ml. K. *pneumoniae* and MRSE bacteria detected together in the blood and wounds were characterized by a high level of resistance to most of the tested antimicrobial drugs.

Many studies described a correlation between high serum PCT levels and gram-negative bloodstream infection [24]. PCT concentrations were significantly higher in patients with positive blood cultures [25]. High blood PCT levels are significantly influenced by gram-negative bacterial endotoxin, which is an obligate lipopolysaccharide of the bacterial wall.

Studies showed that bloodstream infection caused by gram-negative bacteria results in significantly higher PCT levels than gram-positive bacteria. This is due to the fact that gram-negative and gram-positive bacteria recognize Toll-like receptor 4 and Toll-like receptor 2 on the cell surface using lipopolysaccharide and lipoteichoic acid, respectively, and subsequently induce the release of different cytokines and different PCT levels [26].

There are also reports of similar PCT values in gram-negative and gram-positive bacteremia [27]. Oksuz et al. could not demonstrate a statistically significant difference between gram-negative and gram-positive bacteremia in terms of PCT levels [28]. A correlation was established between the PCT value and microflora, provided that the infection site and the bloodstream infection are caused by the same pathogen [29].

According to the literature data, 40–90 % of patients with suspected systemic infection have negative blood culture results [30]. In our study, there was no microbial growth in five cases, while the PCT level was higher than 0.5 ng/ml but lower than 10 ng/ml. The PCT level above 2 ng/ml was observed in 35 subjects, while the pathogen was detected in the blood of only 13 patients.

At the same time, microflora was isolated from the blood of two individuals with a low PCT value (lower than 0.5 ng/ml).

To date, PCT is one of the most studied biomarkers for rational use of antibiotics [31]. PCT threshold values < 0.5 μg/L or reduction by 80–90 % from the peak level are considered a sign of recovery, which is a ground for completing the course of antibiotic therapy. In our study, PCT decreased to threshold values within 5–9 days. In three cases, no decrease in PCT was observed. We assume that the dynamics of PCT concentration during antibacterial therapy can serve as a criterion for the effectiveness of antibiotic use [31–32].

CONCLUSION

In patients with PCT lower than 0.5 ng/ml, gram-positive microorganisms were most often found in the microflora of wounds and sinuses. The proportion of patients with PCT values ⩾ 2 ng/ml and gram-negative bacteria in the focus of infection was higher compared to patients with gram-positive microflora. Nevertheless, the detected high correlation relationship between the microbiocenosis of patients' wounds and procalcitonin values confirms the leading role of gram-positive bacteria in the development of osteomyelitis.

In positive blood cultures, the serum PCT level was, in most cases, higher than 2.0 ng/ml. The presence of gram-negative bacteria in the blood, as well as in the wound, was accompanied by PCT values higher than 10 ng/ml. If the same pathogen was detected in wounds and blood, high resistance of bacteria to most of the tested drugs was noted.

The obtained results showed that a blood test for PCT simultaneously with microbiological studies may be an additional tool in the diagnosis of chronic osteomyelitis.

Conflict of interest *Not declared.*

Funding *None.*

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The article was submitted 16.10.2024; approved after reviewing 09.01.2025; accepted for publication 05.02.2025.

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