Diagnostic value of serum and synovial procalcitonin in acute arthritis: a prospective study of 42 patients

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Abstract

Objective

To determine the diagnostic value of serum and synovial procalcitonin (PCT) for bacterial arthritis and to determine the cellular origin of synovial PCT.

Methods

A prospective study enrolled 42 patients with acute arthritis including 11 bacterial arthritis, 18 rheumatoid arthritis and 13 crystal induced arthritis. Diagnostic values of serum and synovial PCT levels were determined by a immunoluminometric assay (Lumitest® PCT) and compared to those of classical inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, synovial fluid cellularity and both serum and synovial IL-6 and TNF α).
Using fibroblast-like synoviocyte (FLS) cultures derived from rheumatoid arthritis (n = 4) and osteo-arthritis (n = 3) synovium, with or without stimulation by lipopolysaccharid or recombinant streptococcal protein I/II, we attempted to determine whether synovial cells could be a source of PCT.

Results

Serum PCT was the best parameter to distinguish patients with acute bacterial arthritis from patients with crystal induced arthritis or rheumatoid arthritis. In setting of an acute arthritis serum PCT (> 0.5 ng/mL) achieved 55% sensitivity and 94% specificity for the diagnosis of bacterial arthritis, while CRP (> 50 mg/L) had 100% sensitivity but poor specificity (40%). Serum PCT appeared to be higher in patients with septic arthritis resulting from "systemic infection" than in cases resulting from direct inoculation. Synovial PCT was not useful to discriminate between infectious and non infectious arthritis in clinical practice.
PCT could not be detected at significant levels in the conditioned medium from fibroblast-like synoviocyte cultures.

Conclusion

Serum PCTis a poorly sensitive but specific marker of bacterial arthritis. Use of serum PCTin association with CRP could nevertheless be useful in an emergency situation for the diagnosis of bacterial arthritis.

Key words

Acute arthritis, bacterial arthritis, rheumatoid arthritis, crystal-induced arthritis, procalcitonin (PCT), IL6, TNFα

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Introduction

Management of acute arthritis focuses on providing rapid etiologic diagnosis since therapies and outcome vary widely between the different causes of arthritis including rheumatoid arthritis (RA), crystal-induced arthritis (CA) and infectious arthritis. The sequelae of bacterial arthritis (BA) in particular can result in functional disability in 25-50% of cases and be life threatening in 5-15% of patients (1). If a synovial fluid (SF) Gram-stain remains the most important diagnostic procedure, its sensitivity has been estimated to range from 42 to 75% (1, 2). Hence an emergency laboratory indicator of BA would be helpful since antibiotic treatment has to be introduced as soon as possible.

Procalcitonin (PCT), the precursor of calcitonin, is a 116 amino-acid protein which acts as an acute phase protein, but is mostly specifically elevated in severe bacterial or fungal infections (3, 4). PCT is not or mildly elevated in other inflammatory disorders such as vasculitis, viral infections or neoplasm (5-8). These properties, together with a half life of 22-29 hours well suited for daily sampling, have made PCT a convenient tool to monitor serious infections (4, 9-12) or to discriminate bacterial infections from other non bacterial inflammations (6), especially viral infection like meningitis (13, 14). Owing to its specificity, PCT could be very useful to quickly differentiate BA from other forms of acute arthritis.

The first aim of this study was to determine the diagnostic value for BA of serum and synovial PCT and to compare its sensitivity and specificity for the diagnosis of BA. PCT diagnostic value was compared to routine parameters including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and other blood and SF parameters (cell counts, TNFα and IL6 concentrations).

The second aim was to investigate the cellular origin of synovial PCT, as numerous cells are suspected of being possible sources (15-18). Using stimulated and unstimulated fibroblast-like synoviocytes (FLS), we attempted to determine whether these cells could be a source of synovial PCT production.

Patients and methods

Patients

Over a two-year period from January 1999 to January 2001, 42 patients hospitalized for acute arthritis in 8 different French rheumatology departments (Réseau Rhumato Study Group, France) were prospectively enrolled. Biological analyses were performed before administration of any specific therapy and especially of antibiotics, non steroidal anti-inflammatory drugs and steroids. Patients presenting three typical forms of acute arthritis BA, CA and rheumatoid arthritis (RA) were included according to the following criteria:

- BA: SF (Gram stain/culture) or blood cultures positive for bacteria.
- CA: SF positive for crystals (calcium pyrophosphate dihydrate (CPPD) or monosodium urate (MSU) crystals as observed under polarizing red-compensated light microscopy) but blood cultures and synovial cultures negative for bacteria.
- RA: acute arthritis in the presence of confirmed RA (according to ACR criteria), with blood cultures and SF cultures negative for bacteria and light microscopy for crystals.

Fifty-two patients were excluded. Nine patients did not fulfil our inclusion criteria: 2 with reactive arthritis, 1 with Lyme arthritis, 2 with spondylarthritis, 2 with CAwithout identified crystals, 1 with BA without identified bacteria, and 1 with unspecified arthritis. Forty-three patients were excluded on the basis of missing or inadequate samples (serum and SF)

Source of fibroblast-like synoviocytes

Human FLS were harvested from synovial tissue obtained by biopsy at time of joint arthroscopy from patients with osteo-arthritis (OA, n = 3) or RA (n = 4). These 7 patients were not included in the first clinical part of the study.

Methods

Preparation of serum and synovial samples. Serum and SF samples were collected on admission before any treatment and immediately frozen for storage at –80°C. Samples for PCT and cytokine measurements were transported on dry ice and stored at –80°C until

assays were performed in a central laboratory.

Routine laboratory parameters. ESR, leukocyte count, CRP levels and synovial cells count were determined in each hospital at time of admission.

PCT, IL6 and TNFα. Serum and SF PCT, IL6 and TNFα levels were measured using commercially available assay kits. SF samples were centrifuged at 4000g for 10 min, supernatants were collected before PCT and cytokines determinations.
PCT levels were quantified using a sandwich immunoassay with immunoluminometric assay according to the manufacturers' instructions (Lumitest® PCT, Brahms Diagnostica, Berlin, Germany). The lower limit of detection was 0.08 ng/mL and the reference concentration 0.5 ng/mL (cut off valve)
Serum and SF IL6 and TNFα levels were measured using enzyme immunoassays (Immunotech, Marseille, France).

Production of PCT by stimulated and non-stimulated FLS from OA and RA patients
Synoviocyte culture. Human FLS were isolated from the synovial tissues of 7 patients (4 RA, 3 OA) obtained at the time of arthroscopic synovectomy. Briefly, tissues were minced, digested with collagenase (1 mg/mL) in serum-free RPMI 1640 for 3 h at 37°C, centrifuged (130 x g, 10 min, 4°C) and resuspended in M199-RPMI 1640 (1:1) containing L-glutamine (2 mM), penicillin (100 IU/mL), streptomycin (100 µg/mL), amphotericin B (0.25 µg/mL) and 20% heat-inactivated FCS (complete medium). After overnight culture, non-adherent cells were removed and adherent cells were further cultured in complete medium. At confluence, the cells were trypsinized and passaged in 75 cm^2 culture flasks. A homogeneous population of fibroblastic cells, was plated out after 3 to 10 passages (5 x 10^3 cells per well) and grown to confluence in 96-well plates (7-10 days). Prior to activation experiments, the cells were extensively washed with serum-free RPMI 1640, before addition of the appropriate stimuli diluted in the same medium containing antibiotics. Cell number and viability were determined by the MTT test (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide test).
Purification of protein I/II. Recombinant protein I/II of *Streptococcus mutans* OMZ 175 was purified from a pHBsr-1 transformed *Escherichia coli* cell extract by gel filtration and immunoaffinity chromatography.
Cell activation. Human FLS were stimulated with 200 µL of serum-free RPMI 1640 containing protein I/II (50 µg/mL final concentration) or LPS (1 µg/mL) according to previous studies. After incubation for 20 h, the culture supernatants were harvested and used to estimate PCT release.
PCT assay. PCT concentrations in the supernatants were determined with the Lumitest® PCT (Brahms Diagnostica, Berlin, Germany) and the automated Kryptor® PCT (Brahms Diagnostica, Berlin, Germany) using a sandwich immunoassay with an immunoluminometric assay (Brahms Diagnostica). The lower limit of detection was 0.02 ng/mL and the reference concentration 0.5 ng/mL (cut off valve).

Statistical analysis
Results are expressed as median values and ranges. Differences between groups were analyzed using the Wilcoxon-Mann-Whitney rank test for continuous variables. P values below or equal to 0.05 were considered as significant.
Correlations between PCT or CRP and IL6 or TNFα levels were examined by the Spearmann rank test. Sensitivity and specificity were calculated according to standard methods. To evaluate the sensitivity and specificity in the differential diagnosis between infectious (BA) and non infectious (CA + RA) arthritis, ROC (receiver operating characteristics) curves were constructed.

Results

Patients
A total of 42 patients fulfilling the proposed criteria were prospectively enrolled: 11 with BA, 13 with CA and 18 with RA. Clinical characteristics of the patients included are presented in Table I. In the BA group, three had RA and another had also marked leukopenia resulting from chemotherapy. Infections were all bacteriologically proven with 6/11 Gram positive cocci and 5/11 Gram negative rods. The leading sources of infection were classified as either general (i.e. bacteremia arising from a distant source identified or not) or local (i.e. direct inoculation or relapse of a previous infection) and BA was generalized in 6 cases and local in 5. In the CA group there were 8 cases of CPPD crystal arthritis, 4 cases with an acute gout attack and one case of mixed CA(presence of both CPPD and monosodium urate crystals). The 18 RApatients had no history of recent infection or evidence for associated crystal-induced joint effusions.

Table I. Clinical characteristics of the study patients.

	Bacterial arthritis n = 11	Crystal arthritis n = 13	Rheumatoid arthritis n = 18
Mean age (years)	68.4	68.8	62.7
Sex M/F	4/7	7/6	6/12
Mean temperature	38.5°C (37-39.5°C)	38°C (36.8-39°C)	37.6°C (37-38.5°C)
Joints	knee (10)* elbow (1)* shoulder (1)*	knee (11) ankle (1) shoulder (1)	knee (17) shoulder (1)
Crystals			
CPPD	No	9**	No
MSU	No	5**	No

*One patient with 2 joints affected; **one case of mixed crystal arthritis.
CPPD: calcium pyrophosphate dihydrate crystals; MSU: monosodium urate crystals.

Table II. Serum levels of procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood leukocytes, interleukin 6 (IL6) and tumor necrosis factor α (TNFα).

	Bacterial arthritis n = 11	Crystal arthritis n = 13	Rheumatoid arthritis n = 18
PCT(ng/mL)	0.7 (< 0.08-223.6)	< 0.08* (< 0.08-0.69)	< 0.08** (< 0.08-0.61)
CRP(mg/L)	184 (61-453)	110 (4-355)	45** (3.2-323)
ESR (mm/h)	87 (30-120)	60* (3-98)	50* (9-> 120)
Leukocytes (10^3/mm^3)	9.05 (2-17)	8.5 (5.6-12)	8.15 (4.7-16)
IL6 (pg/mL)	142.8 (< 3-3392)	32.7* (< 3-207.1)	69.25 (< 3-278.6)
TNFα (pg/mL)	8.9 (< 3-156)	<3 (< 3-73)	31.05* (5.4-1873)

Results are median values (1st line) and extremes (2nd line). The Wilcoxon-Mann-Whitney test was used for statistical comparison between BAwith the CAand both RAgroups. *p < 0.05; **p < 0.005.

Basal serum levels of PCT, CRP, ESR, IL6, TNFα and blood leukocytes counts

Serum levels of PCT, CRP, ESR, leukocytes, IL6 and TNFα are listed in Table II. Basal levels of serum PCT were higher in the BA group (median value 0.7 ng/mL(range < 0.08 – 223.6) than in the CA(< 0.08 ng/mL (< 0.08 – 0.69) p < 0.05) or RA group (< 0.08 ng/mL, r < 0.08 – 0.61; p < 0.005). Six patients with BA had a serum PCT value > 0.5 ng/ml (55%), while only 1 patient with CA (7.7%) or RA (5.6%) had a PCT value > 0.5 ng/ml. CRP levels were significantly higher in patients with BA (median 184 mg/L) as compared to patients with RA (median 45 mg/L, p<0.005). No difference was found with patients with CA (median 110 mg/L, p = 0.06).

In the BA group, patients with "generalized BA" had higher serum PCT (median 1.8 ng/mL) and CRP levels (median 217 mg/L) than those with "local BA" (median PCT 0.47 ng/mL, CRP 161 mg/L). Values of patients from the BA group are shown in Table III.

Basal SF levels of PCT, cells, IL6 and TNFα

Median SF levels of PCT were higher

Table III. Clinical characteristics (leading source of infection, associated diseases, outcome), bacteriology and serum parameters (PCT, CRP, ESR, TNFα, IL6) of patients with bacterial arthritis.

Form of BA	Leading Source	Bacteria /Isolation	PCT ng/ml	CRP mg/l	ESR mm/h	TNFα pg/ml	IL6 pg/ml	Associated Disease	Outcome
General 1	Cutaneous	*Staphylococcus aureus* Blood	2.67	250	112	< 3	441	No	Favorable
General 2	Cutaneous	*Staphylococcus aureus* Blood	0.93	320	102	17.8	264	RA	Favorable
General 3	Cutaneous	*Staphylococcus aureus* SF	7.91	453	107	42,3	1614	No	Septic shock then Favorable
General 4	Pneumonia	*Streptococcus pneumoniae* SF	223.6	173	79	156	3392	RA	Death (sepsis)
General 5	Not identified	Gram- rod * SF	< 0.08	61	31	< 3	142.8	No	Favorable
General 6	Not identified	*Klebsiella pneumoniae* SF	0.34	184	120	< 3	141.3	Leukopenia	Favorable
Median			**1.8**	**217**	**104.5**	**8.9**	**352.5**		
Local 1	Infiltration	*Staphylococcus aureus* SF	0.47	100	30	< 3	43.3	No	Favorable
Local 2	Relapse	*Salmonella sp* SF	0.25	383	110	47.4	127.2	No	Favorable
Local 3	Relapse	*Proteus mirabilis* SF	0.79	290	87	26.2	406	RA	Favorable
Local 4	Unknown arthritis / Infiltration	*Staphylococcus aureus* SF	0.7	68.7	62	4.7	< 3	No	Favorable
Local 5	Unknown arthritis / Infiltration	*Pseudomonas aeruginosa* SF	<0.08	161	72	8.9	< 3	No	Favorable
Median			**0.47**	**161**	**72**	**8.9**	**43.3**		

* Gram negative rod in the Gram stain but a negative bacterial culture. Procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), tumor necrosis factor α (TNFα), interleukin 6 (IL6), rheumatoid arthritis (RA).

in the BA group (0.22 ng/mL (0.08 – 1.31) than in the RA (<0.08 ng/mL (< 0.08 – 0.6); p< 0.05) or CAgroup (0.09 ng/mL(< 0.08 – 0.88)) but without statistical significance for the latter group (p = 0.28). Only synovial cells counts distinguished BA patients [median 51,000/mm^3 (22000 – 396000)] from both CA(11,200/mm^3 (700 – 96000); p < 0.05) and RA patients (12,800/mm^3 (2500– 72000); p < 0.05). Synovial fluid parameters are reported in Table IV.

Correlations between serum and synovial PCT and pro-inflammatory cytokines (IL6 and TNFα)

Acute phase proteins are synthesized under the control of cytokines, especially IL6 and to a lesser extent TNFα and IL1. Therefore, to determine whether the PCT synthesis occurring in acute arthritis was directly linked to IL6 or TNFα, we attempted to correlate serum and SF PCT with serum and SF IL6 and TNFα levels. PCTand IL6 displayed only a weak positive correlation in serum (r = 0.36, 95% CI 0.047 to 0.68) and no correlation in synovial fluid although the result was close to significance (r = 0.25, 95% CI –0.064 to 0.55). There were no correlations between PCT and TNFα in serum (r = 0.097, 95% CI –0.25 to 0.38) or synovial fluid (r = 0.010, 95% CI –0.2 to 0.41). As a measure of comparison, the best known acute phase protein CRP correlated well with serum IL6 (r = 0.48, 95% CI 0.25 to 0.73) but not with serum TNFα (r = 0.058, 95% CI –0.27 to 0.28).

Sensitivity and specificity of serum and SF parameters for diagnosis of BA

The sensitivity and specificity of serum and SF parameters for discrimination of BA from non bacterial arthritis (CA or RA) were evaluated with different cut-offs and results are presented in Table V. Serum PCT (>0.5ng/ml) achieved a 55% sensitivity and a 94% specificity for the diagnosis of BA while CRP(>50 mg/l) had a 100% sensitivity but a 40% specificity. ROC curves for the sensitivity and the specificity of serum and SF PCT, CRP, ESR and blood leucocytes when BA occurs are shown in Figure 1.

Table IV. Synovial (SF) levels of procalcitonin (PCT), cells, interleukin 6 (IL6) and tumor necrosis factor α (TNFα).

	Bacterial arthritis n = 11	Crystal arthritis n = 13	Rheumatoid arthritis n = 18
SF PCT(ng/mL)	0.22 (< 0.08-1.31)	0.09 (< 0.08-0.88)	< 0.08* (< 0.08-0.6)
Cells (10^3/mm^3)	51 (22-396)	11.2* (0.7-96)	12.8* (2.5-72)
SF IL6 (pg/mL)	38,802 (< 3-333,000)	11,050 (13.4-123,873)	11,519 (165.5-240,870)
SF TNFα (pg/mL)	234 (< 3-2,437)	40.6 (< 3-14,103)	163.6 (27.9-1,679)

Results are the median value (1st line) and extremes (2nd line). TheWilcoxon-Mann-Whitney test was used for statistical comparison of the BAwith the CAand RAgroups. * p < 0.05.

Table V. Sensitivity and specificity of procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and synovial fluid (SF) cells for discrimination of infectious from non-infectious (crystal or rheumatoid) arthritis using different cut-offs.

	Sensitivity (%)	Specificity (%)
Serum PCTng/mL		
- 0.3	72.7	93.5
- 0.5	54.5	93.5
- 0.7	54.5	93.5
CRPmg/L		
- 50	100	40
- 100	81.8	70
- 150	72.7	83.3
ESR mm/h		
- 50	81.8	41.4
- 100	45.4	93.1
SF PCTng/mL		
- 0.1	63.6	61.3
- 0.3	36.4	83.9
- 0.5	36.4	90.3
SF cells		
- 20,000 / mm^3	100	71.4
- 50,000 / mm^3	50	85.7

Table VI. FLS PCT(ng/mL) in the supernatants of synovial cell cultures (basal state or LPS or Prot I/II stimulated) using the Lumitest® and Kryptor® technique.

FLS PCTlevels	Supernatant OA		Supernatant RA	
	Lumitest® n = 1	Kryptor® n = 3	Lumitest® n = 1	Kryptor® n = 4
Basal	0.42	<0.02 (<0.02 – <0.02)	0.31	0.015 (<0.02 – 0.03)
LPS	0.36	<0.02 (<0.02 – 0.04)	0.31	0.015 (<0.02 – 0.03)
Prot I/II	0.29	0.04 (<0.02 – 0.08)	0.30	0.02 (<0.02 – 0.08)

Results are expressed as median and extremes. OA: osteoarthritis, RA: rheumatoid arthritis, LPS: lipopolysaccharide, Prot I/II: recombinant protein I/II of *S. mutans* OM2 175.

Production of PCT by FLS cultures

Basal and stimulated levels of PCT production in FLS cultures ranged from undetectable (<0.02 ng/mL) to a maximum of 0.08 ng/mL (Table VI).

To optimize the detection of FLS PCT, two supernatants, stimulated or not with LPS or protein I/II and derived from one patient with OA and another pt with RA, were tested in parallel and compared using the fully automated Kryptor® PCT technique and the Lumitest® PCT method employed in the clinical part of the study. Results showed higher levels of PCT with the Lumitest® (0.29 to 0.42 ng/mL) as compared to the Kryptor® method (< 0.02 to 0.08 ng/mL).

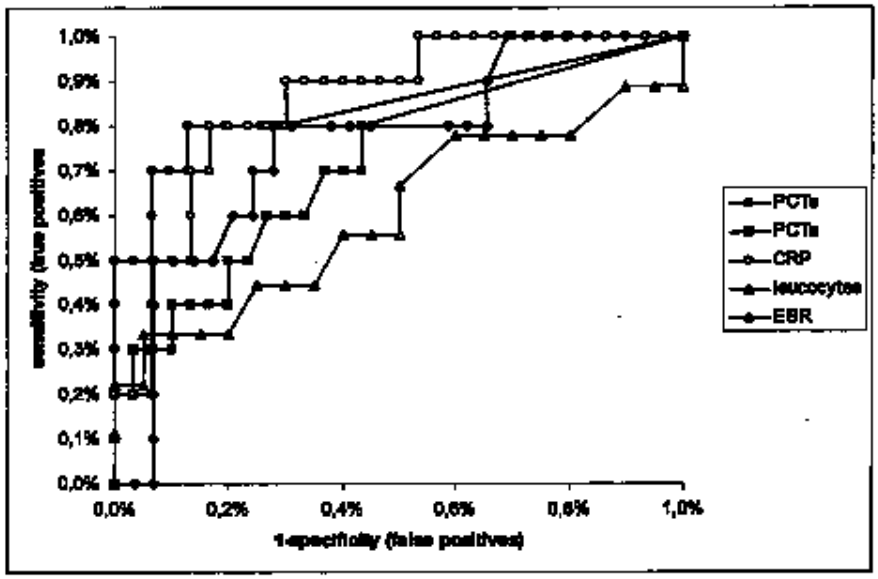

Fig. 1. ROC curves of the sensitivity and the specificity of serum procalcitonin (PCTs), SF procalcitonin (PCTa), CRP, ESR or blood leukocytes in the diagnosis of bacterial arthritis compared to non infectious arthritis (crystal-induced arthritis and rheumatoid arthritis).

Discussion

The first aim of our study was to assess the diagnostic value of serum and synovial PCT in BA. PCT was compared to other inflammatory markers especially those classically used in routine analyses. Serum PCT was the best parameter to distinguish patients with acute bacterial arthritis from both CA and RA patients. The highest values of serum PCTwere reached for BAresulting from systemic infections whereas BA resulting from direct inoculations or relapses triggered only weak serum PCT elevations.

Diagnostic value of serum PCT in bacterial arthritis

The median serum PCT on admission was statistically higher in the BAgroup (0.7 ng/mL) than in the two non infectious arthritis groups (<0.08 ng/mL). PCT variation ranges are quite wide and can reach 1000 ng/mL in septic shock. Persistent high serum PCT levels are associated with a poor prognosis (19, 20). Although we determined PCT levels only on admission, our two highest values were found in one patient who subsequently died from infection and in another with septic shock.

At a cut-off of 0.5 ng/mL, serum PCT has 55% sensitivity and 93.5% specificity for diagnosis of BA. Use of a lower cut-off (0.3 ng/mL) improves the sensitivity without loss of specificity. In this study serum PCT nevertheless appears to be the best marker to discriminate septic arthritis from non-infectious arthritis. Soderquist *et al*. (2), who studied serum PCT in acute arthritis, have found lower values of serum PCTin their BApatients than we did. However, these authors included in their retrospective study post-operative and post-injection BA, which could partly explain this discrepancy. More surprisingly, Soderquist *et al*. found higher levels of serum PCT in their control group including CA patients and we do not have any explanation for this difference, all the more insofar as their levels of CRP in CA patients are quite similar to the present results.

Our results are in accordance with other reports concerning focal infections. PCTlevels, which can reach high values during shock or severe sepsis, seem to lack sensitivity in "local organ related" infections (21-23). In our study, PCT values indeed appear to be higher in "general BA" than in "local BA", although the groups were too small to demonstrate a significant difference. Interestingly, serum PCT level is also high in bacterial meningitis which triggers PCTrelease (13,14), but not in post-operative meningitides (24), where direct inoculation leads to CSF contamination. Whether the low serum PCT results from the lack of bacteremia remains to be clarified, but our results in "local BA" highlight the fact that different mechanisms of infection may lead to different rises in PCT systemic secretion. On the other hand, cases of low PCT during bacteremia have also been reported particularly following infection with Gram + bacteria (11,25) and this point needs further investigation.

Comparison of serum PCT with other inflammatory markers for the diagnosis of BA

Among the other serum parameters we investigated, CRP is certainly the most widely used as a marker for acute inflammation and therefore infections. CRP values were significantly higher in our patients with BA than in those with CA or RA, although there was a large overlap between individual values; statistical difference was only achieved between BA and RA groups. These observations are in agreement with those of Soderquist *et al*., who found CRP determination to be a sensitive but poorly specific marker for infectious arthritis (2). At a cut-off point of 50 mg/L, the specificity of CRP was indeed quite poor (40%) in our study.

Serum levels of IL6 were higher in the BA group than in the CA or RA group, and tend to be more elevated in RA

patients than in CA patients. Serum TNFα were significantly less elevated in BA patients than in RA patients. There was no statistical difference in TNFα levels between BA and CA groups. Inflammatory cytokines and acute phase proteins are not specific for any etiological mechanism of inflammation and previous studies have shown that serum cytokines levels have no diagnostic value to distinguish bacterial from non infectious or viral diseases (6, 26). Moreover cytokines are regulated by complex mechanisms and numerous determinants resulting in large daily variations. The biological kits used for their dosage are also quite heterogeneous and can give different results. These limitations may account for some of the discrepancies between serum cytokine levels reported in the literature (2, 27).

Serum PCT correlated with serum IL6 which might suggest a regulation of serum PCT by pro-inflammatory cytokines, especially IL6 as suggested by previous experimental data (28, 29).

Diagnostic value of synovial PCT and comparison with other synovial inflammatory markers

In our study PCT was detectable in synovial fluids and the highest values were observed among BA patients. PCT levels are generally low during infection in biological fluids such as CSF, pleural fluid or broncho-alveolar washings, the only exception being ascitis fluid where PCT level reaches approximately two-thirds of the plasma level without exceeding plasma levels (30). A possible deleterious role of PCT during infection has been advanced (31, 32) and one may wonder whether SF PCT could likewise participate in arthritic destruction. However in our study, SF PCT is not helpful for the diagnosis of BA

Among other synovial inflammatory markers, only synovial cell count distinguished BA from both RA and CA. Although SF cytokines appeared to be higher in the BA group, there were no statistical differences with respect to the other groups. The interest of SF cytokines in acute arthritis is however subject to debate (27, 33-36).

Cellular source of synovial PCT

The second aim of our study was to determine the cellular source of synovial PCT, since the role and the precise origin of PCT in sepsis remain unclear (15-18). PCT could not be detected or only at very low concentrations in the supernatants of stimulated or non stimulated FLS cultures derived from OA and RA patients. This might exclude these cells as an important source of PCT. In addition experiments using RT-PCR to amplify PCT mRNA from FLS cultures could provide a more precise answer. Unexpectedly, when FLS PCT was assayed and compared using different assays, higher values were obtained with the semi-automated Lumitest® method than with the fully automated and more sensitive Kryptor® method. Hence we cannot rule out that much lower levels of PCT might have been determined in synovial fluid using the Kryptor® technique rather than the Lumitest®, the only method at our disposal at the time of the clinical trial.

The source of SF PCT remains unclear. One could hypothesize a local synthesis by synovial leukocytes under the control of pro-inflammatory cytokines such as IL6 and TNFα, even though we found no correlation between SF PCT and these cytokines in our study.

Our study could appear critisisable in some aspects. First because of the low number of patients included. Yet in order to be an efficient parameter PCT should appear strong enough to discriminate BAfrom non BAwith even a small sample of patients and thus need not a “powerful study”. We had rather focus our work on well defined arthritis: bacterial arthritis with documented infections or crystal and rheumatoid arthritis. We did not include in this study others forms of arthritis such as reactive arthritis, lyme, viral, spondylathropathy, etc. deliberately, in order to have homogenous, well-defined groups and avoid bias in the diagnosis. Indeed if PCT could not discriminate these 3 groups of well-defined arthritis (BA,CA, RA) then this parameter would not be very useful in clinical practise. However having realised this first analysis furthers investigations with newer groups of arthritis such as acute arthritis are needed to clearly define PCT values in acute arthritis.

Some patients did not show elevated values of CRP and ESR which could appear surprising for acute arthritis. Yet our criteria of inclusion did not require a minimal CRP value and thus if these patients presented with an acute arthritis to a physician then they could be included whatever the biological results. Moreover when biological parameters are determined on the very onset of an inflammation the results may appear wrongly as low or normal while raising a few hours after. Only 13% of our patients have a normal CRP, only in the RA/CA groups. We did not precise the duration of evolution of acute arthritis to be eligible for this study and leave the physicians free to include any clinical acute arthritis. In cases of RA the evolution of the arthritis before investigation seems to be longer (days to weeks) than in cases of BAor CA(usually days, and in a few cases weeks). A sub-acute form of arthritis i.e a week-lasting arthritis and thus a less inflammatory form cannot be ruled out. Yet even in cases of sub-acute the problem of septic arthritis must be explored and thus the potential inclusion of such patients remains in our view of interest.

We did not analyse PCT availability and cost in this study though these parameters may be of interest. PCT determination, which theorically could be available in 2.5 to 3 hours is usually obtained only during the “usual laboratory hours” which could limit its interest. A new technique named PCT-Q, which uses the patients serum on a test strip has been recently developed and may be suitable during evenings, nights and week ends as well as directly on the ward. This test was not at our disposition at the time of the study and would need a new study in order to be validated. PCT cost (kryptor) is actually 22 euros, i.e. 36 times the CRP cost 0.61 euros.

In conclusion, our study indicates that serum PCT is a poorly sensitive but specific marker of BA. A low serum PCT does not rule out BA and only positive values of PCT have a diagnostic value in BA. On the contrary synovial PCTis not helpful for the diagno-

sis of BA. Use of serum PCT in association with CRP could nevertheless be of interest in the emergency room, to look for BAin cases of unknown acute arthritis. This interest could be strengthened in case of negative Gram stain or joints where SF is difficult to obtain. Serum PCT levels in other forms of infectious arthritis or in reactive arthritis need to be investigated in order to confirm the diagnostic value of PCT.

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