# Serum procalcitonin measurement for detection of intercurrent infection in febrile patients with SLE

It is sometimes difficult to distinguish infection from disease flare in febrile patients with systemic lupus erythematosus (SLE). Chill, leucocytosis, and increased C reactive protein (CRP) are known to be markers favouring infection.[1] Procalcitonin (PCT) is the precursor of calcitonin and is synthesised in the parafollicular C cells of the thyroid. Serum PCT increases in severe bacterial or fungal infection but does not increase, or increases only slightly, in viral infections.[2 3] The purpose of this study was to evaluate the usefulness of serum PCT in febrile episodes of patients with SLE to distinguish infection from disease flare.

We prospectively enrolled 19 patients with SLE with fever who were admitted to Seoul National University Hospital between October 1998 and April 1999. Fever was defined as an axillary temperature over 38°C. Eleven patients with inactive SLE were enrolled as controls. Blood of the febrile lupus patients was withdrawn three times: on the day of the hospital visit, and after 24 hours and 48 hours. Another sample was withdrawn two weeks after defervescence to control infection or because of a decrease in lupus activity. At the detection of fever, blood cultures and other necessary cultures were performed with complete blood count, Westergren erythrocyte sedimentation rate (ESR), CRP, serum anti-dsDNA, complements (C3, C4), urine analysis, serum creatinine, and chest *x* ray examination.

The patients were divided into groups on the basis of viral infection, non-viral infection, and lupus flare. Lupus flare was defined by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[4] as an increase of more than three points compared with the SLEDAI of the patient one month before the febrile period. Serum PCT was measured by an immunoluminometric assay (LUMItest, Brahms Diagnostika, Berlin). Twelve lupus patients were shown to have infection (nine non-viral, three viral infections) and seven patients had lupus flare. Non-viral infections consisted of urinary tract infection (n=3), sinusitis (n=1), tuberculosis (n=1), scrub typhus (n=1), pseudomembranous colitis (n=1), aspergillosis (n=1), and nocardiosis (n=1). Viral infections were upper respiratory infection (n=2) and gastroenteritis (n=1).

The white cell count was higher in the group with non-viral infection than in the group with lupus flare (p=0.015, table 1). Westergren ESR increased in 89% of the groups with viral and non-viral infection and in all members of the group with lupus flare. There was no difference between the Westergren ESRs of the groups with viral and non-viral infection and lupus flare during the early febrile period (p=0.32). CRP increased in 92% of the group with infection and 89% of the group with lupus flare. CRP tended to be higher in the group with non-viral infection than in the groups with viral infection or lupus flare, but this did not reach significance (p=0.98).

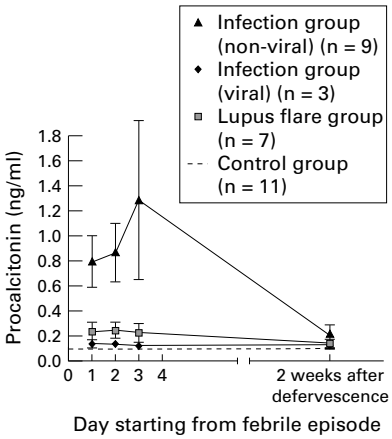


*Figure 1 Mean procalcitonin levels during and after febrile episode. Bars denote standard error.*

Serum PCT in the group with non-viral infection tended to increase continuously or rise gradually in the early febrile period (fig 1). Serum PCT levels in the early febrile period were significantly higher in the group with non-viral infection (mean (SD), 0.98 (0.12) ng/ml) than in the group with viral infection (0.13 (0.04) ng/ml, p<0.01), the group with lupus flare (0.24 (0.18) ng/ml, p<0.01), and the controls (0.12 (0.03) ng/ml, p<0.01). There was no statistical difference in the PCT levels of the groups with viral infection or lupus flare and the control group (p=0.12). After defervescence the serum PCT level was 0.21 (0.18), 0.13 (0.04), 0.14 (0.08) ng/ml in the group with non-viral infection, the group with viral infection, and the group with lupus flare, respectively. None of the values were significantly different from the control group (p=0.86, 0.49, 0.58, respectively).

New serological markers to distinguish lupus flare from infection have been investigated in an attempt to differentiate infection with lupus flare. Serum PCT is normally almost undetectable (<0.1 ng/ml) and not influenced by kidney function. Dandona *et al* found that after injecting endotoxin intravenously, PCT increased suddenly at six hours and maintained a plateau for more than 24 hours.[5] Recently, the stimulation of peripheral blood mononuclear cells with lipopolysaccharide was found to increase PCT mRNA transcription.[6] PCT levels in autoimmune disease were first studied by Eberhard *et al*, who showed that the PCT increased in vasculitic patients with infection (1.93 (1.19) ng/ml) and decreased after control of the infection (0.63 (0.62) ng/ml).[7] PCT did not increase in patients with Wegener's granulomatosis upon disease aggravation but increased with combined infection.[8]

Our study is the first to observe serum PCT changes in lupus patients with fever and defervescence prospectively. In our study lupus patients with bacterial or fungal infection had higher serum PCT levels than those with viral infections and a higher level than the controls. We tried to determine the serum PCT changes during the febrile period by measuring serial samples. Serum PCT in the group with non-viral infection tended to increase continuously or rise gradually in the early febrile period (fig 1). The PCT values varied among the non-viral group and serious infections, such as aspergillus pneumonia, showed higher values than urinary infection or sinusitis (data not shown). The pitfalls of PCT as a marker for infection are that it may not increase or increase only slightly in viral infection. Our study showed that there was no difference between the serum PCT of the group with viral infection and the control group.

CRP is useful for detecting and differentiating infections in lupus.[9] CRP rises earlier and is more sensitive than ESR. In this study, CRP tended to increase in the case of non-viral infection, compared with viral infection or lupus flare, but this did not reach statistical significance. Our results indicate that during the early febrile period, serum PCT increased significantly in patients with SLE with non-viral infection compared with patients with lupus flare. Serum PCT decreased after defervescence. These results suggest that serum PCT helps in detecting bacterial or fungal infections during the early febrile period in SLE.

*Table 1 Baseline data of 19 patients with systemic lupus erythematosus (SLE) during the early febrile period. Results are shown as means (SD)*

| Group | Sex (M:F) | Age | White cell count ($10^9$/l) | ESR (mm/1st h) | CRP (mg/l) |
|---|---|---|---|---|---|
| Non-viral infection (n=9) | 1:8 | 25.6 (13) | 12.9 (8.8)* | 82.0 (27.7) | 73.7 (78.6) |
| Viral infection (n=3) | 1:2 | 25.7 (3.5) | 5.7 (4.9) | 60.0 (49.8) | 39.7 (21.5) |
| Lupus flare (n=7) | 0:7 | 33 (8.2) | 3.9 (1.4) | 97.7 (31.5) | 54.7 (61.3) |
| Controls (n=11) | 1:10 | 43.2 (13.7) | — | — | — |

*p=0.015 compared with the group with lupus flare.

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1 Kraus A. Fever in systemic lupus erythematosus. In: Klippel JH, Dieppe, eds. *Rheumatology.* 2nd ed. Barcelona: Mosby, 1998:7.8.3.
2 Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515–18.
3 Karzai W, Oberhoffer M, Meier-Hellmann A, Reinhart K. Procalcitonin-a new indicator of the systemic response to severe infections. Infection 1997;25:329–34.
4 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of SLEDAI. Arthritis Rheum 1992;35:630–40.
5 Dandona P, Nin D, Wilson MF, Aljada A, Love J, Assicot M, *et al.* Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1974;79:1605–8.
6 Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, *et al.* Procalcitonin

expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis-related cytokines in vitro. J Lab Clin Med 1999;134:49–55.
7 Eberhard OK, Haubitz M, Brunkhorst FM, Kleim V, Koch KM, Brunkhorst R. Usefulness of procalcitonin for differentiation between activity of systemic autoimmune disease (systemic lupus erythematosus/systemic antineutrophil cytoplasmic antibody-associated vasculitis) and invasive bacterial infection. Arthritis Rheum 1997;40:1250–6.
8 Moosig F, Csernok E, Reinhold-Keller E, Schmitt W, Gross WL. Elevated procalcitonin levels in active Wegener's granulomatosis. J Rheumatol 1998;25:1531–3.
9 Hind CRK, NG SC, Feng PH, Pepys MB. Serum C-reactive protein measurement in the detection of intercurrent infection in Oriental patients with systemic lupus erythematosus. Ann Rheum Dis 1985;44:260–1.

## Effect of daily corticosteroid treatment on CRP response to hip or knee replacement in patients with RA

Serum C reactive protein (CRP) is an acute phase reactant which may be continuously increased in patients with persistently active rheumatoid arthritis (RA),[1] or raised only temporarily to a high concentration for a few days as a normal response to uncomplicated hip or knee replacement in patients with osteoarthritis or RA.[2 3] CRP usually decreases in patients with RA when inflammatory activity is treated with daily low dose corticosteroid. This prompts the question whether the CRP response to hip or knee replacement is decreased in patients with RA taking a daily low dose of oral corticosteroid compared with those not taking corticosteroid. This is an important issue because CRP is used as an index to indicate postoperative complications. In this letter we compare the CRP response to hip or knee replacement in two groups of patients with RA: those taking and those not taking oral low dose corticosteroid.

Sixty patients (47 women, 13 men) fulfilling the American Rheumatism Association 1987 criteria for RA,[4] treated at the Rheumatism Foundation Hospital, Heinola, in 1999, underwent hip or knee replacement. Fifty two patients were seropositive. The group receiving prednisolone comprised 44 patients, mean age 62 (SD 8.5) years. The prednisolone doses were as follows: four patients received <5 mg daily, 37 had 5–10 mg daily, and three had 12.5–30 mg daily. The patient group not receiving prednisolone comprised 16 patients, mean age 59 (13.4) years.

The CRP concentration was measured by the Randox, United Kingdom, immunoturbidimetric assay. The magnitude of the CRP response was measured by assessing the difference between measurements taken preoperatively and during the first one to two days postoperatively (the time of the peak CRP level[3]) in both patient groups. The CRP responses in the respective groups were compared and statistically evaluated with the Mann-Whitney U test. In the group not receiving prednisolone the preoperative median CRP level was 12 (interquartile range (IQR) 5–26) mg/l, and at day 1 or 2 postoperatively the median CRP had risen to 80 (IQR 53–112) mg/l. In the group in which patients were taking prednisolone the preoperative median was 14 (IQR 6–38) mg/l, the postoperative median 62 (IQR 41–100) mg/l. The difference in CRP response to the operation between the groups was not significant, p=0.15 (fig 1). None of the patients had bacterial infection or substantial haematoma after the operation.

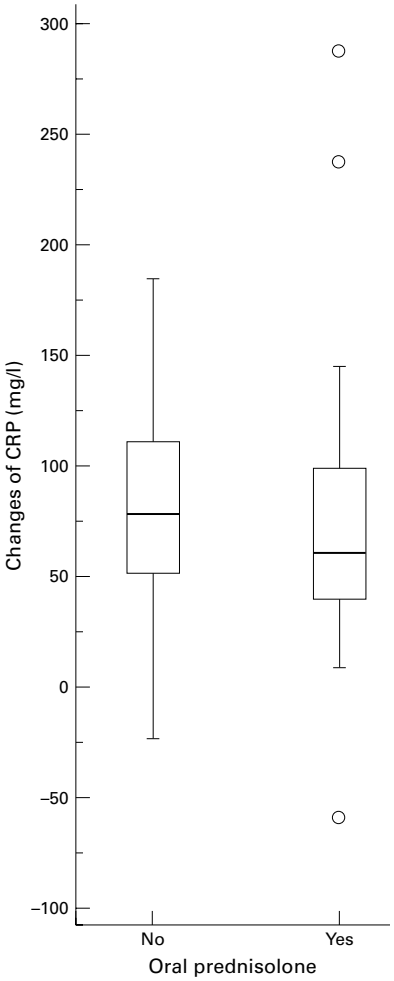


*Figure 1 Box and whisker plots show the postoperative C reactive protein (CRP) response to hip or knee replacement in 16 patients with RA not receiving prednisolone and 44 patients with RA receiving continuous prednisolone.*

The rise in CRP concentration in response to hip or knee replacement was slightly, but not significantly, smaller in patients with RA receiving than in those not receiving prednisolone. Increased CRP concentration was a normal phenomenon in the first few days after hip or knee replacement in these patients with RA and was not altered by low dose prednisolone treatment. This study affords no information as to the CRP response in the presence of postoperative complications, because no such case was encountered. However, we recommend further measures if the CRP concentration remains raised for several days postoperatively and does not decrease steadily.

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1 Dixon JS, Bird HA, Sitton NG, Pickup ME, Wright V. C-reactive protein in the serial assessment of disease activity in rheumatoid arthritis. Scand J Rheumatol 1984;13:39–44.
2 Larsson S, Thelander U, Friberg S. C-reactive protein (CRP) level after elective orthopedic surgery. Clin Orthop 1992;275:237–42.
3 Laiho K, Mäenpää H, Kautiainen H, Kauppi M, Kaarela K, Lehto M, *et al.* Rise in serum C reactive protein after hip and knee arthroplasties in patients with rheumatoid arthritis. Ann Rheum Dis 2001;60:275–7.
4 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

## Lumbar spondylodiscitis secondary to *Enterobacter cloacae* septicaemia after extracorporeal shock wave lithotripsy

Infections of the lumbar spine may affect either the intervertebral disc or the vertebral body. Most infections of the intervertebral disc occur as an extension of vertebral osteomyelitis or direct inoculations during diagnostic or surgical procedures, or include urinary tract infections and septicaemia. This paper reports a case of L5-S1 spondylodiscitis secondary to *Enterobacter cloacae* septicaemia after extracorporeal shock wave lithotripsy (ESWL).

A 52 year old man presented with side pain, pollakiuria, haematuria, and nocturia. He had been treated with ciprofloxacin for acute pyelonephritis and nephrolithiasis as an outpatient. One week later, the patient was admitted to hospital by the urology department with symptoms of left side pain, fever, chills, shaking, and dysuria. Right renal and right ureter distal lithiasis and right hydronephrosis due to the lithiasis were diagnosed. One week after ESWL the patient was sent to the physical medicine and rehabilitation clinic with chills, shaking, high fever, and low back pain complaints. Lumbar movements were found to be restricted. There was an increase in severe pain at rest. The patient could not stand or walk. No neurological deficit was present. Body temperature was 39°C, pulse 110 beats/min, blood pressure 130/70 mm Hg, breathing 20 breaths/min.

Laboratory findings were as follows: haemoglobin 133 g/l, packed cell volume 0.31, white blood cells $18\times10^9$/l, platelets $316\times10^9$/l, erythrocyte sedimentation rate 110 mm/1st h, antistreptolysin O 25 IU, C reactive protein 12.3 mg/l, rheumatoid factor negative. Urea was 14 mmol/l of urea, creatinine 170 µmol/l. Glucose and electrolytes were normal and serum aspartate aminotransferase was 80 U/l, serum alanine aminotransferase 44 U/l, lactate dehydrogenase 321 U/l, total bilirubin 22 µmol/l, direct bilirubin 10 µmol/l. A considerable number of leucocytes and erythrocytes were noticed in urine microscopy. *Enterobacter cloacae* was isolated from blood and urine. The isolated pathogen was sensitive to ceftriaxone and amikacin.