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ORIGINAL STUDY

The significance of interleukin-6 and lactate in the synovial fluid for diagnosing native septic arthritis

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Aim of this study was to evaluate the role of synovial interleukin-6 and synovial lactate for predicting native septic arthritis.

We analyzed retrospectively synovial fluid parameters (interleukin-6, total-protein, glucose, lactate, synovial-fluid-white-blood-cell-count) of 62 patients with culture-verified native septic arthritis and compared them to 57 patients with acute aseptic arthritis. Receiver-Operating-Characteristic-curves were calculated to determine the 'Area-under-the-curves' (AUC), the best thresholds and the corresponding likelihood-ratios.

The best parameter for diagnosing septic arthritis was synovial lactate (AUC = 0.864, sensitivity = 74.5%, specificity = 87.2%), followed by synovial interleukin-6 (AUC = 0.803, sensitivity = 92.5%, specificity = 64.1%) and the synovial-fluid-white-blood-cell-count (AUC = 0.782, sensitivity = 71.2%, specificity = 84.9%).

Synovial lactate levels above 10 mmol/l almost proofed septic arthritis (interval-Likelihood-Ratio = 20.4), synovial interleukin-6 levels lower than 7000 pg/ml almost ruled out infection (interval-Likelihood-Ratio = 0.12). If none of these thresholds are met, physicians should estimate disease probability by the simultaneous use of the interval-Likelihood-Ratios of synovial lactate, synovial interleukin-6 and synovial-fluid-white-blood-cell-count.

Keywords : septic arthritis, inflammatory markers, interleukin-6, synovial fluid, lactate.

INTRODUCTION

Today it is still a major challenge to diagnose septic arthritis, although many markers in serum and synovial fluid have been investigated (*6*). But each of these markers is either more specific and less sensitive for septic arthritis (peripheral white blood cell count, synovial fluid white blood cell count), or more sensitive and less specific (C-reactive Protein, erythrocyte sedimentation rate, procalcitonin) (*6,23*). Additionally, less than 65% of synovial gram stains of infected joints have a conspicuous microscopy (*6,36*) and negative cultures of the synovial fluid and the blood do not rule out infection (*24*). The time interval between onset of septic arthritis and diagnosis is inversely related to clinical outcome. Researchers investigate the levels of inflammatory markers during septic arthritis in order to find sensitive and specific markers, which enable physicians to diagnose septic arthritis immediately.

It is known that Interleukin-6 (IL-6) is elevated in many body fluids like serum in sepsis (*34*) and

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liquor cerebrospinalis during bacterial infections of the brain (*15*). It exists evidence that IL-6 in the synovial fluid is a very good marker for predicting periprosthetic joint infections (*8,17*) and is more accurate than serum CRP, peripheral white blood cell count (pWBC) and synovial fluid white blood cell count (SFWBC) (*8*). Lögters *et al* reported an excellent diagnostic potential of synovial IL-6 for predicting an infectious joint, but he included only nine patients with septic arthritis and six of them had an endoprosthesis at the affected joint (*22*). Although it is generally accepted that synovial IL-6 is elevated during septic arthritis, only one study, that included only 9 patients with septic arthritis, deals with the topic of 'IL-6 as inflammatory marker in septic arthritis'. It exists no clinical trial about synovial IL-6 levels which included only patients with native septic arthritis. Our hypothesis was that IL-6 could be an excellent parameter for differing between native septic arthritis and acute aseptic arthritis.

The purpose of our study was :

(1) to determine the diagnostic potential of synovial IL-6 levels for predicting native septic arthritis in a larger clinical study ;

(2) and to analyse which parameters in the synovial fluid are the most accurate to distinguish between septic or acute aseptic arthritis.

PATIENTS AND METHODS

From November 2006 until June 2013 we examined synovial fluid parameters of 119 patients who presented at the emergency unit of our hospital and underwent arthrocentesis because of suspected native septic arthritis. 53 septic patients were also included in a prior study which compared inflammatory markers in septic and gouty arthritis (*20*). This is a retrospective trial without personal data, therefore we did not require any approval of the Ethics Review Committee of the Technical University of Munich, Germany. No blood test and no joint aspiration was done for the sole purpose of this study, no diagnostic or therapeutic regimen was directly influenced. The standard operating procedure in suspected arthritis is already established, thus providing a solid basis for routine data acquisition. The study was conducted in accordance to the Declaration of Helsinki. The mean age of study participants was 69.9 ± 14.1 years with a range of 22 to 96 years. 65 women (55%) and 54 men (45%) took part in this trial. We aspirated synovial fluid from 83 knee joints, 19 hip joints, 13 shoulder joints, 2 elbow joints and 2 upper ankle joints.

Inclusion criteria for this study were suspicion of septic arthritis on admission because of three out of five classic symptoms of infection in any joint: pain, redness, swelling, heat and impaired range of motion.

Indication for joint aspiration was suspicion of septic arthritis. Synovial fluid was obtained under strictly aseptic conditions and was examined for biomarker concentrations in a routine clinical laboratory. Microbiological testing was done by a microbiologist.

A positive bacteriological culture is the "gold standard" to diagnose septic arthritis (*31*). In order to investigate the diagnostic accuracy of synovial IL-6 in bacterial arthritis, we minimized the number of patients with falsely diagnosed infectious arthritis by including only patients with a positive microbiologic culture of the synovial fluid.

62 patients suffered from culture-verified native septic arthritis. Patients with periprosthetic joint infections or culture-negative septic arthritis were excluded from this clinical trial. Culture-verified septic arthritis was compared to 57 patients with acute aseptic arthritis (9 suffered from reactive arthritis, 4 from rheumatoid arthritis and 46 from activated osteoarthritis). Osteoarthritis was diagnosed by a physician and affirmed by a radiologist; a joint infection was ruled out in the control-group during the stay at the hospital. Patients with culture-verified septic arthritis and with acute aseptic arthritis showed at least three out of five infection symptoms and were suspected to suffer from septic arthritis.

In the synovial fluid IL-6 ($IL\text{-}6_{syn}$), total protein (TP_{syn}), glucose (Glc_{syn}), lactate (Lac_{syn}) and SFWBC were examined.

If the measured parameter level was below detectable limit of the assay, for statistical analysis the value was set to the minimal detectable value.

Statistical analysis was performed by using SPSS for Windows software (SPSS 17.0, Inc., Chicago, IL). The calculation of the arithmetical mean and the use of the T-Test for independent variables allowed the search for inflammatory markers, whose arithmetical mean differed highly significant ($p < 0.01$) between septic arthritis and acute aseptic arthritis. Receiver operating characteristic (ROC-) curves, Area under the curves (AUCs), cutoff-values, sensitivities (SE), specificities (SP), positive likelihood-ratios (+LR), negative likelihood-ratios (-LR) and interval likelihood-ratios were calculated for each parameter to determine its significance in predicting sep-

tic arthritis. Likelihood-ratios show the change from pre-test to post-test disease probability (*4,26*) and have a greater clinical utility than sensitivity, specificity, positive and negative predictive values and ROC curves (*11*). +LRs > 10 denote clinical importance and mostly clinical significance as well as a –LR < 0.1 (*4*). Interval likelihood-ratios exemplify more of the information in collected data than likelihood-ratios. Thus interval likelihood-ratios enable clinicians to interpret test results more accurately and to make more accurate clinical decisions (*4*). The optimal cutoff-value was calculated by maximizing sensitivity and specificity (Youden's J statistic). A professional statistician approved this statistical approach.

RESULTS

Demographics, types of bacteria and localization of septic arthritis

In 62 patients (33 females, 53%) a culture-verified native septic arthritis was detected. Mean age was 70.4 12.5 years (range 22 to 96 years).

The prevailing pathogens of septic arthritis were *Staphylococcus aureus* (n = 24), *coagulase negative staphylococci* (n = 11) and *ß-hemolytic streptococci* (n = 7) (a detailed list of isolated types of bacteria is shown in Table I). In seven infected joints two bacterial species were identified.

The most frequently infected joints in the culture-verified group were the knee (n = 38), followed by the hip (n = 14), the shoulder (n = 7), the upper ankle joint (n = 2) and the elbow (n = 1).

Mean values of inflammatory parameters

The arithmetical mean of the synovial fluid markers IL-6, SFWBC, lactate, TP_{syn} and Glc_{syn} were significantly increased during septic arthritis compared to acute aseptic arthritis ($p < 0.01$). Scatter plots show the distribution of inflammatory marker levels in septic arthritis and in the control group (Fig. 1).

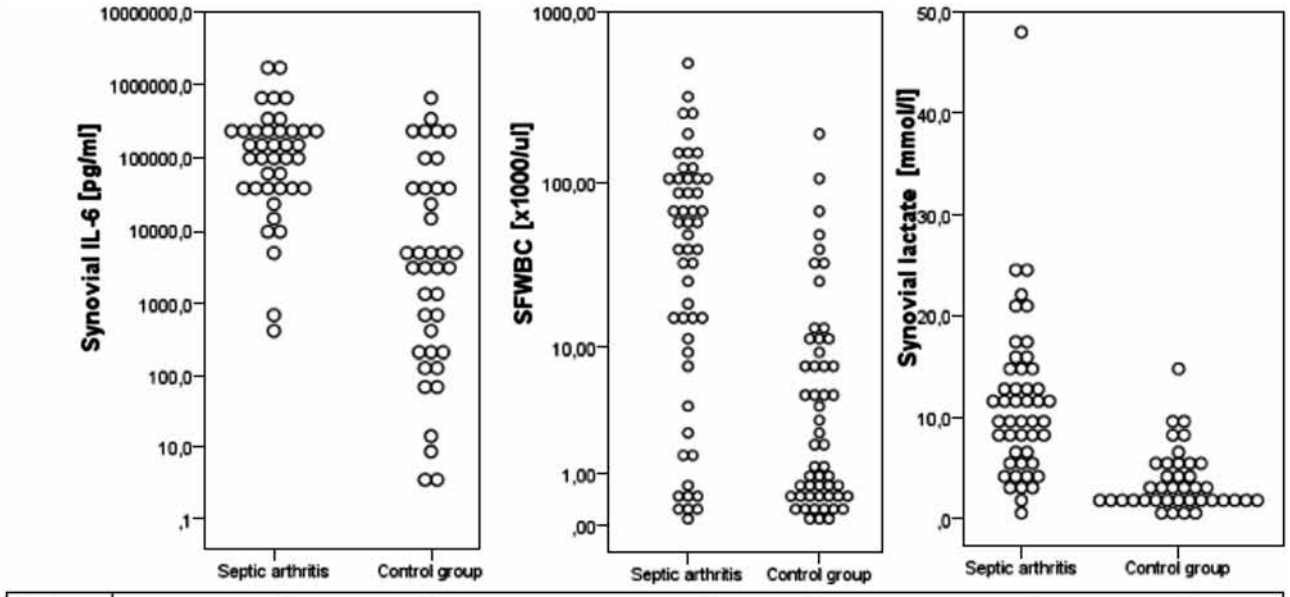
Receiver Operating Characteristic Curves

We calculated the ROC-curves of inflammatory markers with significantly increased mean values to ascertain which ones have the highest diagnostic potential for predicting septic arthritis. ROCs and their corresponding AUCs were calculated to evaluate the differences in concentration in native septic arthritis and acute aseptic arthritis. These ROCs allowed us to determine the sensitivity, the specificity, the positive likelihood-ratio and the negative likelihood-ratio of each inflammatory parameter. The AUCs of all depicted images were highly significant ($p < 0.01$).

The inflammatory markers with the highest potential to differ between septic arthritis and acute aseptic arthritis were $lactate_{syn}$ (AUC= 0.864, SE = 74.5%, SP = 87.2%), $IL\text{-}6_{syn}$ (AUC = 0.803, SE = 92.5%, SP = 64.1%) and the SFWBC (AUC = 0.782, SE = 71.2%, SP = 84.9%) (Table II). The AUC, cutoff-values, sensitivity, specificity, positive likelihood-ratio, negative likelihood-ratio as well as the interval likelihood-ratio for each parameter are listed in Table II and Table III.

Table I. — Number and percentage of different pathogens in culture-verified septic arthritis

Bacteria	**Number (Percentage)**
Staphylococci	37 (54%)
Staphylococcus aureus	*26 (38%)*
Coagulase negative staphylococci	*11 (16%)*
Streptococci	9 (13%)
B-hemolytic streptococci gr. A	*1 (1.4%)*
B-hemolytic streptococci gr. B	*3 (4.3%)*
B-hemolytic streptococci gr. C	*1 (1.4%)*
B-hemolytic streptococci gr. G	*2 (2.9%)*
Streptococcus pneumonia	*2 (2.9%)*
Gram negative bacteria	14 (20.3%)
Escherichia coli	*4 (5.8%)*
Pseudomonas aeruginosa	*2 (2.9%)*
Salmonella enterica	*2 (2.9%)*
Enterobacter faecium	*1 (1.4%)*
Proteus mirabilis	*1 (1.4%)*
Citrobacter koseri	*1 (1.4%)*
Acinetobacter lwoffii	*1 (1.4%)*
Morganella morganii	*1 (1.4%)*
Achromobacter oxylosoxidans	*1 (1.4%)*
Other types of bacteria	
Peptostreptococcus spp.	*4 (5.8%)*
Enterococcus faecium	*1 (1.4%)*
Enterococcus faecalis	*4 (5.8%)*



Number	n= 40	n= 39	n= 52	n= 53	n= 47	n= 39
Mean	239664	60234	73.5	12.7	11.4	3.7
Median	118500	3380	45.0	1.9	10.1	2.5
T-test	p= 0.008		p= 0.00004		p= 0.00000009	

Fig. 1. — Scatter plots of synovial IL-6, synovial fluid white blood cell count (SFWBC) and synovial lactate. The arithmetical means of these parameters are statistically significant increased during septic arthritis.

Table II. — AUCs, cutoff-values, sensitivity, specificity, positive and negative likelihood ratio for inflammatory markers in culture-verified septic arthritis compared to acute aseptic arthritis

			Markers in the synovial fluid		
	IL-6 [pg/ml]	**TP_syn [g/dl]**	**Glc_syn [mg/dl]**	**Lactate [mmol/l]**	**SFWBC [10^3/µl**
AUC	0.803 (0.702-0.903)	0.698 (0.599-0.798)	0.701 (0.597-0.804)	0.864 (0.785-0.942)	0.782 (0.689-0.874)
Cutoff-value	7000	4.3	40	6.2	14.4
Sensitivity	92.5% (80.1-97.4)	55.6% (42.4-68.0)	56.6% (43.3-69.1)	74.5% (60.5-84.8)	71.2% (57.7-81.7)
Specificity	64.1 (48.4-77.2)	75.0% (61.8-84.8)	83.0% (69.9-91.1)	87.2% (73.3-94.4)	84.9% (73.0-92.2)
+LR	2.58 (1.68-3.96)	2.22 (1.31-3.77)	3.33 (1.70-6.52)	5.81 (2.52-13.39)	4.71 (2.43-9.14)
-LR	0.117 (0.04-0.36)	0.59 (0.42-0.83)	0.52 (0.38-0.73)	0.29 (0.18-0.48)	0.34 (0.22-0.53)

AUC = area under the curve ; +LR = positive likelihood ratio ; -LR = negative likelihood ratio. Values in brackets are the 95%-confidence interval.

Table III. — Interval likelihood ratio of synovial inflammatory markers for predicting septic arthritis

Interleukin-6 [pg/ml]	**Interval likelihood ratio**
> 50 000	3.29 (1.71-6.33)
7000 – 50 000	1.62 (0.65-4.04)
< 7000	0.12 (0.04-0.36)
Lactate [mmol/l]	**Interval likelihood ratio**
> 10	20.43 (2.89-144.35)
4.3 – 10	1.36 (0.70-2.66)
< 4.3	0.21 (0.10-0.42)
SF WBC [x10³/µl]	**Interval likelihood ratio**
> 50	8.49 (2.73-26.42)
25 – 50	1.43 (0.48-4.21)
< 25	0.45 (0.31-0.65)

Values in brackets are the 95%-confidence interval.

DISCUSSION

The most frequently isolated pathogens in septic arthritis were staphylococci and streptococci. This is in accordance with earlier findings (*33*). Similar findings for types of bacteria and frequency of affected joints in septic arthritis were published recently (*18*). These facts show that our data originate from a representative sample of the affected population.

The inflammatory marker synovial lactate is known to be raised unspecifically in different kinds of joint diseases like rheumatoid arthritis (*29*), osteoarthritis (*16*) and trauma (*5*). Nevertheless, synovial lactate showed in this study the highest discriminatory potential in predicting septic arthritis and performed much better than the SFWBC (Fig. 2). Especially synovial lactate levels higher than 10 mmol/l almost proofed septic arthritis (interval likelihood-ratio = 20.43) and septic arthritis was very unlikely, if synovial lactate levels were below 4.3 mmol/l (interval Likelihood-ratio = 0.21) (Table 3). It has been reported that an increase of synovial lactate concentrations are useful for predicting septic arthritis (*6,13,19*), but its diagnostic potential has been underestimated (*6*) and not been further investigated (*25*). Three studies used for synovial lactate cutoff-values from 10 mmol/l to 12 mmol/l (*3,28,30*), whereas the most recent study used a cutoff-value of 0.05 mmol/l (*13*). These clinical studies have in common that they reported about the high diagnostic accuracy of synovial lactate, but included a maximum of 27 patients with septic arthritis. Carpenter et al. claimed that synovial lactate may be helpful to rule in or rule out

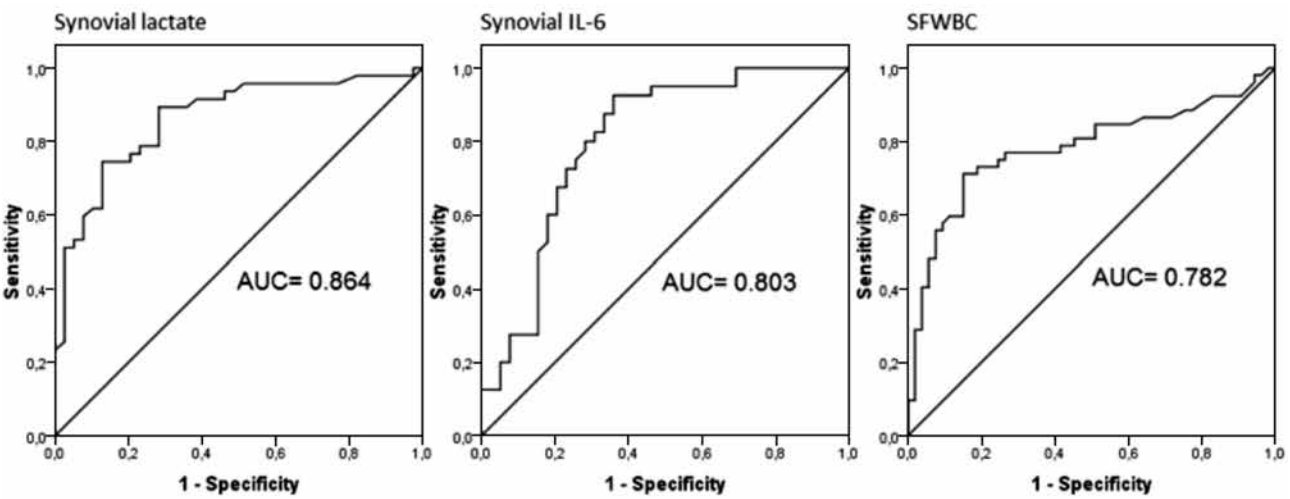


Fig. 2. — Receiver Operating Characteristic curves of various inflammatory parameters in culture-verified septic arthritis compared to acute aseptic arthritis. Synovial lactate was the marker with the highest diagnostic potential, followed by synovial IL-6 and the synovial fluid white blood cell count (SFWBC).

septic arthritis and that future diagnostic trials should compare its diagnostic potential to other inflammatory markers (*6*). This clinical trial showed that synovial lactate is the inflammatory marker with the highest diagnostic potential for diagnosing septic arthritis (AUC = 0.864). Its interval likelihood-ratios are more useful for calculating the change from pre-test to post-test disease probability of septic arthritis than the interval likelihood-ratios of the other inflammatory markers.

Three smaller clinical studies, that included 14 and 31 patients with periprosthetic joint infections have revealed for synovial IL-6 a high diagnostic accuracy for diagnosing periprosthetic joint infections (*8,17,21*). Deirmengian et al. reported for synovial IL-6 a diagnostic accuracy of 1.00, suggesting that the examined population has been too small to obtain representative results (*8*). Lögters *et al* reported for synovial IL-6 an AUC of 0.951 for diagnosing septic arthritis, but only 9 patients with septic arthritis were included (*22)*. Our trial included 62 patients with culture-verified native septic arthritis and synovial IL-6 had good diagnostic potential for predicting septic arthritis (AUC = 0.803). Additionally, IL-6 was the most sensitive tool for diagnosing septic arthritis compared to the remaining biomarkers. Synovial IL-6 levels below 7000 pg/ml diminished the post-test probability of septic arthritis considerably (interval likelihood-ratio = 0.12), thus it was the best parameter to rule out septic arthritis. The studies named above used for IL-6 in the synovial fluid cutoff-values in a range from 625 pg/ml to 13350 pg/ml (*8,17,22*). The ideal cutoff-value for synovial IL-6 in this study was 7000 pg/ml, which is nearly exactly in the middle of this range. But it has been described that synovial IL-6 is also increased during several types of inflammatory arthritis (*9,12*). This may have let to the decreased specificity of synovial IL-6 in this study. 21 patients with septic arthritis had synovial IL-6 levels above 100000 pg/ml. Increased IL-6 levels stimulate osteoclasts and induce the synthesis of matrix metalloproteinases (MMP), leading to bone resorption and cartilage destruction (*1,7,14,32, 37*). Thus may be followed by irreversible joint damage and may be responsible for the considerable morbidity after septic arthritis. Synovial IL-6 was the second best inflammatory marker behind synovial lactate, but performed worse than in smaller studies (*8, 22*).

The SFWBC showed the third best diagnostic potential for predicting septic arthritis. Low SFWBCs did not rule out infection, but a SFWBC above $50 \times 10^3/\mu l$ made infection very likely (interval likelihood-ratio = 8.49). Thus the SFWBC is a useful parameter to confirm native septic arthritis. This is in accordance with McGillicuddy et al. (*27*) and with Bedair et al. who claimed that the SFWBC is useful for diagnosing infectious arthritis and periprosthetic joint infections (*2*), whereas Mathews *et al* decided that the SFWBC is not usable to exclude or diagnose septic arthritis (*25*). The SFWBC was only a fair test for predicting septic arthritis (AUC = 0.782), the sensitivity of the SWBC was too low to reliably exclude a joint infection. The intervals of the interval likelihood-ratio coincided with previous proposals to use cut-off-values of $25.0 \times 10^3/\mu l$ and $50.0 \times 10^3/\mu l$ (*6*), but other cutoff-values have also been suggested in current literature (*6*). As a result, further inflammatory markers have to be taken into consideration, when septic arthritis is suspected.

In this study inflammatory markers in serum had a lower diagnostic potential than synovial fluid markers for diagnosing septic arthritis; this is in accordance with prior findings, too (*6*). Nevertheless, CRP concentrations in the blood seem to be the best serum inflammatory marker for predicting infectious joints (*10, 35*).

We acknowledge that we had limitations during this study. One restriction to our study was the retrospective study design. Furthermore, patients suffering from culture-negative septic arthritis and periprosthetic joint infections were excluded from this study. This was done to minimize false diagnoses of septic arthritis, but could have biased our test-results. Moreover we could not identify all biomarkers from every patient. The reasons for that were sicca-puncture and low volume of aspirated synovial fluid. The 95%-confidence intervals of the interval likelihood-ratios are relatively wide due to the smaller number of patients in each interval. Further studies about native septic arthritis will evaluate the accuracy of our results. The strength of

this study was that the gold standard for diagnosing septic arthritis had been used and that concurrently a large number of patients with septic arthritis were included.

CONCLUSION

This was the first larger clinical trial that examined simultaneously the role of synovial IL-6 and synovial lactate for predicting native septic arthritis. Lactate levels in the synovial fluid have the highest diagnostic potential for predicting septic arthritis. Synovial lactate levels above 10 mmol/l lead to a substantial increase of disease probability, thus it is concluded that synovial lactate should play a more important role in daily clinical work than it is practiced today. In addition, it is concluded that synovial IL-6 levels below 7000 pg/ml make septic arthritis very unlikely. We detected in the synovial fluid more than 1000-fold elevated IL-6 levels, compared to high pathognomonic IL-6 levels in serum. We conclude that therapeutic lowering of IL-6 levels in the synovial fluid during septic arthritis may be an ideal approach to reduce morbidity. The significance of $lactate_{syn}$ and $IL\text{-}6_{syn}$ in septic arthritis should be further prospectively investigated and further studies have to show if synovial lactate levels differ also when compared to spondylitis ankylosans and rheumatoid arthritis.

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