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Interleukin-6 in two-stage revision arthroplasty

WHAT IS THE THRESHOLD VALUE TO EXCLUDE PERSISTENT INFECTION BEFORE RE-IMPLANATATION?

The purpose of this study was to evaluate whether the serum level of interleukin 6 (IL-6) could be used to identify the persistence of infection after the first stage of a two-stage revision for periprosthetic joint infection. Between 2010 and 2011, we prospectively studied 55 patients (23 men, 32 women; mean age 69.5 years; 36 to 86) with a periprosthetic joint infection. Bacteria were identified in two intra-operative tissue samples during re-implantation in 16 patients. These cases were classified as representing persistent infection.

To calculate a precise cut-off value which could be used in everyday clinical practice, a 3 x 2 contingency table was constructed and manually defined.

We found that a serum IL-6 ≥ 13 pg/mL can be regarded as indicating infection: its positive-predictive value is 90.9%. A serum IL-6 ≤ 8 pg/mL can be regarded as indicating an absence of infection: its negative predictive value is 92.1%.

The serum IL-6 level seems to be a reasonable marker for identifying persistent infection after the first stage of a revision joint arthroplasty and before attempting re-implantation.

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The diagnosis of periprosthetic joint infection (PJI) is difficult,1,2 but it is even harder to exclude persistent infection before the second (re-implantation) stage of a two-stage revision arthroplasty. As the reported rate of re-infection or persistent infection is up to 30%, the ability to be able to exclude this is desirable.3-5

The value of standard markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and the white blood cell (WBC) count in synovial fluid in the detection of persistent infection has been described. Shukla et al6 showed that CRP was still elevated before re-implantation in 22 patients (27.5%) in whom the infection had been eradicated. CRP and ESR did not help to exclude persistent infection, whereas the WBC in synovial fluid was helpful. Mortazavi et al13 and Kusuma et al17 were unable to identify any marker that was useful in the exclusion of persistent infection.

The use of IL-6 to diagnose a PJI has been confirmed by several studies.8-10 To the best of our knowledge, however, its ability to identify persistent infection before re-implantation has not been investigated.

The aim of the present study was to measure the IL-6 levels in serum and synovial fluid before the second (re-implantation) stage of a two-stage revision joint arthroplasty for PJI, in order to establish a cut-off value, which could be used in daily clinical practice in an attempt to improve the accuracy of diagnosis of persistent infection.

Patients and Methods

Definition of PJI. In our study patients were only included if an identical organism was found in at least two periprosthetic cultures. At least three tissue samples were taken.11

In accordance with the criterion mentioned above, persistent infection was also defined by at least two positive cultures with an antibiotic spacer in place, from at least three tissue samples obtained during the second-stage procedure before insertion of the new prosthesis.

Between 2010 and 2011, a total of 55 patients (total hip arthroplasty (THA) n = 31, total knee arthroplasty (TKA) n = 24), for whom two-stage revision for PJI was planned, fulfilled this criterion and were included in the study. The mean age of the 23 male and 32 female patients was 69.5 years (36 to 86). All patients were referred to us from other hospitals. The mean interval between implantation and the diagnosis of a PJI was 2.7 years (0.8 to 4.3). In all, 36 of these patients had undergone at least one previous revision. Our protocol consisted of removing the prosthesis and implanting an antibiotic-loaded bone cement spacer (Refobacin Revision bone cement,
Biomet, Warsaw, Indiana; 1 g gentamycin and 1 g clindamycin / 40 g cement). Patients then received at least 14 days of intravenous antibiotics followed by at least four weeks of oral antibiotics. After an interval of 14 days without antibiotics and before re-implantation, we measured the patient’s CRP and serum IL-6 levels as well as the IL-6 level and WBC count in their synovial fluid. On each occasion the same laboratory system for IL-6 was used (ImmunoLite, Siemens Medical Solutions Diagnostics GmbH, Eschborn, Germany). All hips and knees were re-implanted during the second-stage procedure.

Statistical analysis. Statistical analyses were performed using IBM-SPSS Statistics v.22 (IBM, Armonk, New York). The distributions of non-normally distributed parameters between infectious and non-infectious cases were compared using the non-parametric Mann–Whitney U test. P-values were considered exploratory, not confirmatory. No adjustment for multiple testing was performed. An overall significance level was not determined and cannot be calculated. Receiver operating characteristic (ROC) analyses were performed to evaluate the diagnostic performance of each marker. The diagonal line in the ROC diagram corresponds to a random guess in the diagnosis of infection.

The area under the diagonal line is equal to 0.5. We calculated the area under the ROC curve (AUC) with 95% confidence intervals (CI). This represents the probability that the marker value of a randomly chosen infectious case ranks higher than the marker value of a randomly chosen non-infectious case. For parameters with significant diagnostic performance (IL-6 and CRP in serum), threshold values for optimal diagnosis of infection were determined using classification and regression tree (CART) analyses.

Using the determined cut-off values, the diagnostic performance of the respective marker was evaluated as follows: the sensitivity is the proportion of cases with elevated results among all infectious cases; the specificity is the proportion of cases with values which were not elevated among all non-infectious cases; the positive predictive value (PPV) is the proportion of infectious cases among all cases with elevated results; the negative predictive value (NPV) is the proportion of non-infectious cases among all cases with no elevation of their results.

Results

In all, 16 patients (29.1%) were subject to persistent infection: the same organism was identified pre-operatively in 12 of these patients. In the other four patients the infecting organism changed from staphylococcus Staph. epidermidis to candida albicans (n = 1), to Staph. epidermis (n = 2) and from Staph. epidermis to Escherichia (E.) coli (n = 1).

The mean serum IL-6 level before re-implantation was significantly different between patients with a persistent infection (17 pg/mL; 3 to 89) and those without (3 pg/mL; 2 to 29; p < 0.001, Mann–Whitney U test). The ROC curve for serum IL-6 is shown in Figure 1a. Patients with a spacer in situ had serum IL-6 levels with an AUC of 0.896 (95% CI 0.797 to 0.994). An AUC of 1 demonstrates an ideal test with a 100% sensitivity and 100% specificity, whereas an AUC of < 0.5 indicates that the diagnostic test is less useful.

To calculate a precise cut-off value which could be used in everyday clinical practice, a 3 x 2 contingency table was constructed from CART analysis (Table I).

This showed that an IL-6 value of ≥ 13 pg/mL in serum can be regarded as indicating infection. An IL-6 value of ≥ 8 pg/ml in serum can be regarded as indicating an absence of infection. In the range of 9 pg/ml to 12 pg/ml for IL-6, no conclusions can be drawn. Only five of the 54 patients (9.26%) were in this group. In one patient the IL-6 value could not be included, because of problems with the laboratory system. Therefore this value was deleted for statistical analysis.

The calculations derived from the 3 x 2 contingency for IL-6 in serum table are shown in Table I. They have a sensitivity of 66.67%, a specificity of 89.74%, a PPV of 90.91% and a NPV of 92.11%.

There was a significant difference in the median serum CRP before replantation between patients who had a persistent infection (1.65 mg/dl; IQR 0.8 to 3.6) and those who did not (0.6 mg/dl; 0.51 to 1.8; p = 0.015, Mann–Whitney U test). The ROC curve for serum CRP is shown in Figure 1b.

The AUC for serum CRP was 0.704 (95% CI 0.551 to 0.858). A CRP value in serum of > 2.5 mg/dl can be regarded as indicating infection. A CRP value in serum of ≤ 2.5 mg/dl can be regarded as indicating the absence of infection. A 2 x 2 contingency table for serum CRP found a sensitivity of 43.75%, a specificity of 92.31%, a PPV of 70% and a NPV of 80% (Table II).

There was no significant difference between the median level of IL-6 in the synovial fluid of patients with a persistent infection (3740 pg/mL; IQR 638 to 31260) and those without (2198 pg/mL; 1300 to 4580; p = 0.529, Mann–Whitney U test). Therefore no useful cut-off value could be found. The ROC curve for the level of IL-6 in synovial fluid is shown in Figure 1c. The AUC for IL-6 in synovial fluid was 0.562 (95% CI 0.330 to 0.794).

There was no significant difference between the median WBC count in the synovial fluid of patients with a persistent infection (949/μl, IQR 272 to 3289.5) and those without (466/μl, 219 to 2008; p = 0.578, Mann–Whitney U test). Therefore no useful cut-off value could be found. The ROC curve for WBC count in synovial fluid is shown in Figure 1d. The AUC for the WBC count in synovial fluid was 0.556 (95% CI 0.356 to 0.757).

Table III shows the median values and interquartile ranges for CRP in serum, IL-6 in serum, WBC count in synovial fluid and IL-6 in synovial fluid for patients with and without persistent infection before re-implantation. Combining the CRP in serum, WBC count and IL-6 level in synovial fluid with IL-6 level in serum did not improve the diagnostic accuracy.
There were no significant differences between THA and TKA before re-implantation (Table IV).

Table V shows the organisms found in the first stage.

### Discussion

The reported rate of failure to eradicate infection after a two-stage revision is up to 30%.3,4,12-14 As is known from diagnosing PJI, two identical positive cultures from periprosthetic tissue are the strongest proof of existing periprosthetic joint infection.11 In accordance with these findings, we required two identical positive cultures as the reference standard for confirming persistent infection. Unfortunately, in clinical practice this level of proof is obtained too late: positive cultures acquired at the time of
re-implantation can lead to further revision due to persistent or recurrent PJI.15

This study provides a cut-off value for the serum level of IL-6 which indicates persistent infection after the first stage of a two-stage revision total joint arthroplasty. There are, however, several limitations to our study, not least the small number of patients included. Our high re-infection rate allowed certain threshold values to be applied but these values could differ with a lower re-infection rate. We also recognise that the measurement of IL-6 is not available in all hospitals. Berbari et al16 have also shown that the level of IL-6 is a highly accurate marker for PJI. Comorbidities and other medical circumstances were not taken into account. Additionally we did not distinguish between Gram-positive and Gram-negative infections. It has been reported that patients with a Gram-negative bacteraemia have higher levels of IL-6.17 Because of the small number of Gram-negative infections in our series, we could not investigate this topic by statistical analysis. It would be of interest to see how IL-6 values in serum change with time after the removal of an infected implant. We only determined IL-6 values once because of the cost involved. The cost of a serum CRP is about €2 (£1.57): IL-6 costs about €22. For serum CRP a cut-off value could also be found, which contrasts with the results of Kusuma et al:7 this marker was not, however, as accurate as a serum IL-6.

In conclusion, this study shows that the level of serum IL-6 can help to differentiate between patients with and without persistent infection after first stage revision and placement of an antibiotic spacer for PJI. In combination with the use of other inflammatory parameters, the likelihood is that the detection of persistent infection prior to re-implantation can be improved. Further studies with larger groups of patients are needed to confirm our results.

References


