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Staged Revision for Knee Arthroplasty Infection

What Is the Role of Serologic Tests Before Reimplantation?

Elie Ghanem MD, Khalid Azzam MD, Mark Seeley MD, Ashish Joshi MD, MPH, Javad Parvizi MD, FRCS

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Abstract Erythrocyte sedimentation rate and C-reactive protein are common preoperative diagnostic markers for prosthetic joint infection but their prognostic role before reimplantation has yet to be defined. We therefore determined the prognostic value of erythrocyte sedimentation rate and C-reactive protein performed before second-stage reimplantation for the treatment of infected total knee arthroplasty (TKA). We studied 109 patients who had undergone two-stage revision TKA for sepsis from 1999 to 2006. Receiver operating characteristic curves were constructed to determine the discriminatory value of erythrocyte sedimentation rate and C-reactive protein before reimplantation in predicting persistent infection. Twenty-three of the 109 patients (21%) required revision surgery for recurrence of prosthetic joint infection. The receiver operating characteristic areas under the curve suggested erythrocyte sedimentation rate and C-reactive protein poorly predicted persistent infection after TKA reimplantation. Cutoff values could not be obtained because of the high variance. We reached similar conclusions regarding the change in erythrocyte sedimentation rate and C-reactive protein levels from time of resection. More accurate diagnostic tools are needed to support clinical judgment in monitoring infection progress and thus deciding whether to proceed with TKA reimplantation.
Level of Evidence: Level II, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

E. Ghanem, K. Azzam, M. Seeley, A. Joshi, J. Parvizi (✉)
Rothman Institute of Orthopedics at Jefferson, Thomas Jefferson University, 925 Chestnut Street, Philadelphia, PA 19107, USA
e-mail: research@rothmaninstitute.com

Introduction

TKA decreases pain and improves quality of life in the majority of patients with durable long-term results. However, infection remains a common cause of failure after TKA that can occur in up to 2% of cases [4, 14]. Two-stage reimplantation is considered the gold standard for treating infected TKA with more than a 90% success rate reported [8, 10, 11, 13]. The procedure entails removal of all hardware and foreign material, insertion of an antibiotic-impregnated spacer, and administration of an extended course of intravenous antibiotics. Successful treatment revolves around eradicating infection and maintaining a functional joint. The timing and criteria for reimplantation that result in minimal reinfection rates remain controversial.

Although serologic tests, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are important in screening for periprosthetic joint infection (PJI) [2], their role before reimplantation of a resected TKA remains poorly defined. A normal or progressively decreasing ESR and CRP have been considered favorable indicators for reimplantation in the absence of clinical signs of PJI [6, 12]. Other investigators have proceeded with reimplantation only when knee aspirate cultures were negative for bacterial growth [11, 16]. Nonetheless, the prognostic role of serology before reimplantation has yet to be defined.

We therefore attempted to define threshold values using receiver operating characteristic (ROC) curves for serologic markers, including ESR and CRP, that can direct the surgeon in the decision-making process of whether to pursue or forego reimplantation. We further investigated the ambiguous role of aspiration performed only in patients with a clinical suspicion of persistent PJI before reimplantation.

Materials and Methods

We retrospectively reviewed the hospital and clinical records of all patients prospectively enrolled in the revision total joint arthroplasty database at our institution who underwent two-stage resection arthroplasty for infected TKA between January 1999 and June 2006. Our cohort consisted of a consecutive series of 109 patients (56 men, 53 women) with an average age of 68 years and body mass index of 32.3 kg/m^2. The diagnosis for index primary arthroplasty was degenerative osteoarthritis in 101 patients, rheumatoid arthritis in three patients, posttraumatic arthritis in four, and hemophiliac arthritis in one. Periprosthetic infection occurred after primary arthroplasty in 84 cases, whereas the remaining 25 patients were previously revised for aseptic mechanical failure. Although 35 patients underwent irrigation and débridement with retention of components for PJI before admission, all patients underwent their first resection arthroplasty at our institution. Infection was classified as acute, acute hematogenous, or chronic according to the classification by Tsukayama et al. [23]. Thirty-four patients presented acutely, four cases had hematogenous seeding, whereas the remaining 71 had chronic infection. Three of the four hematogenous infections resulted from cellulitis involving the same lower extremity that was operated on, and the fourth patient developed osteomyelitis of the jaw just before manifesting symptoms of PJI. All patients were treated with reimplantation after the first-stage resection. The minimum followup after reimplantation was 2 years (mean, 2.8 years; range, 2.1–7.6 years). Three patients died as a result of causes unrelated to their surgery before 2 years; they were free of infection at their last followup. Institutional Review Board approval was obtained before initiation of our prospective study and all patients gave consent to participate in the study.

Patients were diagnosed with periprosthetic infection if they fulfilled one of the following criteria: (1) an abscess or sinus tract was communicating with the joint space; (2) positive preoperative aspiration culture on solid media; or (3) two or more positive intraoperative cultures or one positive culture on solid media in conjunction with the presence of gross purulence. In patients with negative cultures, PJI was diagnosed according to an elevated cell count and differential of the aspirate fluid [21] and abnormal serology (ESR greater than 30 mm/hr, CRP greater than 1 mg/dL). A total of 88 patients had positive intraoperative cultures at the time of resection and were confirmed to be infected according to the third criteria listed previously. Of the remaining 21 patients with negative intraoperative cultures, four had a positive aspirate culture and presence of gross purulence intraoperatively, whereas two other patients had a sinus tract communicating into the joint. Fifteen patients had negative cultures and a diagnosis of PJI was made based on an elevated cell count and differential and abnormal serology. The most common organisms retrieved from the preoperative aspirate fluid and/or intraoperative cultures were: methicillin-sensitive Staphylococcus aureus (MSSA; 19%), methicillin-resistant S. aureus (MRSA; 13%), methicillin-resistant S. epidermidis (MRSE; 13%), methicillin-sensitive S. epidermidis (MSSE; 13%), Streptococcus species (12%), Gram-negative organisms (8%), mixed flora (5%), Corynbacterium striatum (1%), and no growth (16%).

Preoperative serological testing using ESR and CRP before resection was performed. The CRP level was quantitated using turbidimetric techniques (Beckman Coulter, Brea, CA), whereas the ESR was measured using an automated analyzer (Mini-Ves, Plymouth, MN). Two or more intraoperative specimens were sent for aerobic and anaerobic cultures during the resection and reimplantation procedures. The mean preoperative ESR and CRP of the general cohort obtained within 1 month (range, 1–29 days) of resection arthroplasty were 79 mm/hr (range, 9–132 mm/hr) and 11.8 mg/dL (range, 0.5–49 mg/dL), respectively. The average ESR and CRP before reimplantation were 49 mm/hr (range, 5–115 mm/hr) and 2.13 mg/dL (range, 0.5–13.8 mg/dL), respectively. The serologic tests were performed at a mean of 13 days (range, 0–44 days) before reimplantation and 94 days (range, 43–555 days) after resection arthroplasty.

All patients underwent resection arthroplasty with removal of implants and cement with thorough débridement of devitalized tissues and insertion of antibiotic cement spacer block. Four grams vancomycin and 3.6 g tobramycin were added to 40 g cement in each patient. The patients were then treated with 6 weeks of antibiotics tailored according to the sensitivity profile of the cultured organism. The most commonly used antibiotics included vancomycin, rifampin, cefazolin, and ciprofloxacin. After the last round of intravenous antibiotic treatment, the patients were examined and any signs of persistent wound drainage or fevers/chills indicated a high clinical suspicion of lingering infection. Arthrocentesis of the knee was performed on a select group of 34 patients before reimplantation as a result of a high clinical suspicion of

unrelenting infection. Revision of the cement spacer block and redébridement was performed in 16 of these 34 patients as a result of persistent purulent drainage and/or systemic symptoms of fever and chills. These 16 patients were treated with another course of 6 weeks of intravenous antibiotics and were subsequently reimplanted at a later date. Intraoperative tissue cultures taken during spacer exchange were positive in only three of the 16 patients. Arthrocentesis was performed in this subgroup of patients prior to the second-stage procedure as well as in those with persistent swelling or severe joint pain. A decision to proceed with the second-stage reimplantation procedure was concluded based on the absence of clinical signs of infection and a negative aspirate culture that was performed on the select group of patients. Serologic testing, including both ESR and CRP, was then performed as close as possible to the date of reimplantation.

The second-stage procedure consisted of reimplanting cemented knee revision components at an average of 107 days (range, 45–558 days) from the time of resection. Reimplantation was postponed for three patients who developed postoperative complications, including cerebrovascular accident, massive myocardial infarction, and aspiration pneumonia that required medical optimization before reimplantation. A constrained condylar system was implanted in 79% of the patients, whereas the remaining 23% received a hinged construct. Intraoperative cultures at the time of reimplantation were positive in 12 cases (11%); the organisms cultured were MRSE (five patients), MSSE (three patients), Proteus mirabilis (two patients), MRSA (one patient), and Pseudomonas aeruginosa (one patient). All 12 patients had a least two positive cultures with growth on solid media. In seven cases, an organism was cultured different from the one found at the time of resection. These patients were treated with 6 weeks of appropriate intravenous antibiotics. Only two patients underwent further surgery to control the infection, whereas the remaining 10 cases were infection-free at latest followup.

It is quite difficult to define persistent infection in a patient who underwent resection arthroplasty and then received intravenous antibiotics for 6 weeks. Some virulent pathogens can still be isolated on solid culture media at the time of reimplantation, whereas others require means of retrieval more sophisticated than conventional culture that are not routinely used [22]. In the latter group, persistent PJI may manifest at a much later date after reimplantation. Hence, we defined two modes of failure resulting from persistent infection: (1) the patient required subsequent revision surgery for PJI after reimplantation; or (2) the presence of a positive intraoperative culture of specimens obtained during the second-stage procedure.

The mean and 95% confidence interval of ESR and CRP before initial resection and reimplantation procedures were determined and compared using the t test (normal distribution of data) among patients who successfully completed their treatment and those who failed with relapsing PJI. The proportion of systemic disorders and comorbid conditions that can elevate ESR and CRP, including inflammatory diseases (rheumatoid arthritis, ankylosing spondylitis, and gout), chronic renal failure, hepatitis, and metastatic malignancy, were compared between the successfully treated and failed groups using chi square analysis [7, 18, 20]. ROC curves, which depict the relation between true-positive (sensitivity) and false-negative (1-specificity) cases, were constructed for ESR and CRP before reimplantation. The area under the curve (AUC) was calculated for each of these variables. An AUC of 1 demonstrates an ideal test with a 100% sensitivity and specificity, whereas an AUC of less than 0.5 indicates the diagnostic test is less useful. The sensitivity, specificity, and predictive values were calculated for arbitrarily chosen ESR and CRP cutoff values before reimplantation to predict recurrence of infection. A similar analysis was performed for the difference of the ESR and CRP values before resection and before reimplantation in an attempt to compensate for the possible bias introduced as a result of the different timeframes when the serologic tests were obtained. All statistical analyses were performed using SPSS, Version 13 (SPSS Inc, Chicago, IL) and SAS statistical software package (SAS Institute Inc, Cary, NC).

Results

Two-stage exchange arthroplasty eradicated the infection in 86 of the 109 patients (79%) in this cohort. Twenty-three patients (21%) were revised for recurrent PJI at an average of 20.4 months (range, 2.8–43.9 months) after reimplantation. Patients presented acutely with fever, chills, or purulent drainage within a few months after surgery or reported chronic knee pain and swelling 1 to 2 years postoperatively. Fifteen patients underwent resection of their reimplanted components and intravenous antibiotic treatment, whereas the remaining eight cases underwent multiple rounds of irrigation and débridement with retention of components to control the infection. Methicillin-resistant organisms (MRSA and MRSE) were cultured from the majority of relapsing infections (57%). The organism cultured during the revision procedure for infection was different from the organism isolated from the initial resection arthroplasty in only six of the 23 cases.

The mean ESR ($p = 0.83$) and CRP ($p = 0.43$) before the second-stage procedure of patients who were revised for recurrent PJI were similar to those of patients who were successfully treated and infection-free at latest followup (Table 1). The mean difference in ESR and CRP values at

Table 1. The means and standard deviations of ESR and CRP before reimplantation

Variables	Recurrence of PJI		p Value
	Yes	No	
ESR mean	50.9 (32.76)	49.2 (29.59)	0.83
CRP mean	2.62 (3.30)	2.04 (2.14)	0.43
ESR (Δ) mean	26.0 (36.76)	29.2 (34.49)	0.70
CRP (Δ) mean	8.71 (11.43)	9.40 (10.60)	0.80

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; PJI = prosthetic joint infection; Δ = value at resection − value at reimplantation.

time of reimplantation and resection for patients who became reinfected and those who were successfully treated was similar (Table 1). There were no differences in the proportion of patients with inflammatory diseases (p = 0.23), chronic renal failure (p = 0.36), and hepatitis (p = 0.91) between patients who failed or were successfully treated. Although our cohort included 26 patients with a history of previously treated malignancy, we could not identify any patient with active metastatic malignancy at the time of resection or reimplantation.

The sensitivity, specificity, and predictive values for the ESR levels of 30 mm/hr and 45 mm/hr and CRP levels of 1 mg/dL and 2 mg/dL ranged from 20% to 80% in diagnosing persistent infection in the group of patients who required revision surgery (Table 2). A difference of 5, 10, and 15 mm/hr between ESR levels at time of resection and reimplantation also showed poor sensitivity, specificity, and predictive values. Similar results were observed for a difference in CRP of 1 mg/dL and 2 mg/dL between levels drawn before reimplantation and resection (Table 2).

Given the low AUC for both ESR and CRP before reimplantation and their differences from resection, cutoff values with an optimal balance of sensitivity and specificity could not be calculated. The AUC of the ROCs for ESR and CRP values (Fig. 1A–B) collected before reimplantation were

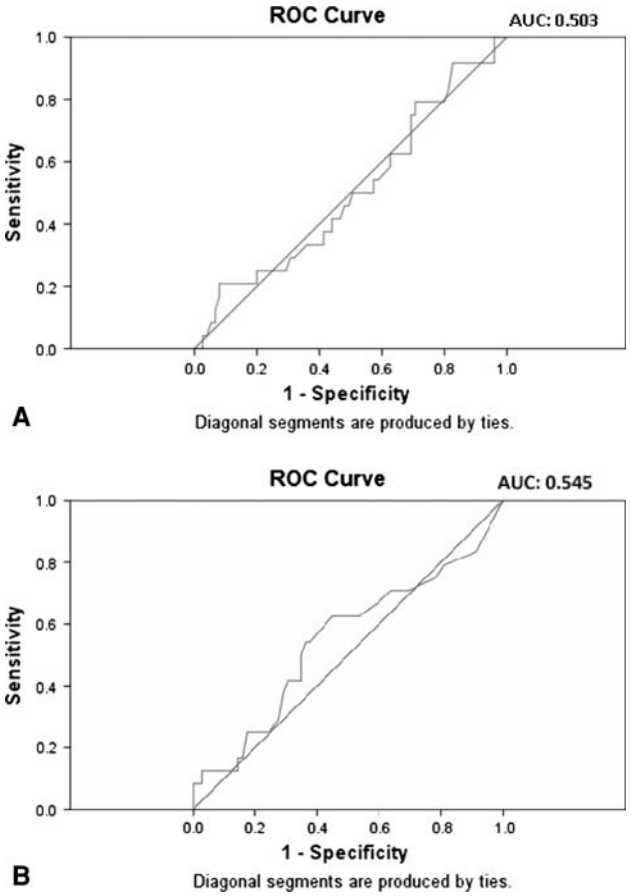

Fig. 1A–B (**A**) Receiver operating characteristic (ROC) for erythrocyte sedimentation rate before reimplantation and (**B**) ROC for C-reactive protein before reimplantation is shown. The straight line indicates the demarcation below, which is an area under the curve (AUC) of 0.5.

0.503 (confidence interval [CI], 0.369–0.638; p = 0.96) and 0.545 (CI, 0.40–0.687; p = 0.51), respectively, when using the first mode of failure as an end point. The AUC obtained for the difference between ESR at time of reimplantation and resection (Fig. 2A–B) was 0.481 (CI, 0.346–0.616;

Table 2. Cutoff values for ESR and CRP in detecting persistent infection

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ESR greater than 30 mm/hr	65.2 (42.7–83.6)	32.4 (22.0–44.3)	23.1 (13.5–35.2)	75.0 (60.0–90.0)
ESR greater than 45 mm/hr	45.8 (25.6–67.2)	51.4 (39.4–63.2)	23.4 (12.3–38.0)	74.5 (62.6–86.5)
CRP greater than 1 mg/dL	66.7 (44.7–84.3)	39.7 (28.0–52.3)	28.1 (16.9–41.5)	77.1 (59.9–89.6)
CRP greater than 2 mg/dL	29.2 (12.6–51.0)	72.5 (60.4–82.5)	26.9 (11.6–47.8)	74.6 (62.5–84.5)
Δ ESR greater than 5 mm/hr	70.8 (48.9–87.3)	24.0 (14.3–35.3)	22.9 (13.9–34.5)	72.0 (50.6–87.9)
Δ ESR greater than 10 mm/hr	66.7 (47.8–85.5)	25.3 (15.9–36.7)	22.2 (13.3–33.6)	70.4 (49.8–86.3)
Δ ESR greater than 15 mm/hr	62.5 (40.6–81.2)	29.3 (19.0–39.6)	22.1 (12.2–31.9)	71.0 (51.9–85.8)
Δ CRP greater than 1.5 mg/dL	70.8 (52.6–89.0)	14.5 (7.2–25.0)	22.4 (13.6–33.4)	58.8 (32.9–81.6)
Δ CRP greater than 2 mg/dL	62.5 (43.1–81.2)	23.2 (13.9–34.9)	22.1 (12.9–33.8)	64.0 (42.5–82.0)

Ranges shown in parentheses; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; Δ = value at resection − value at reimplantation.

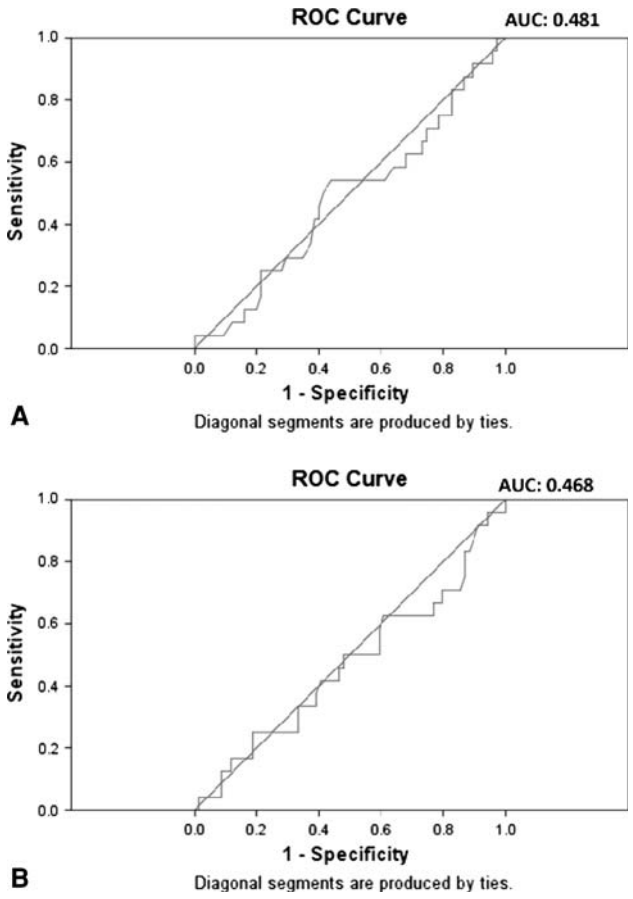

Fig. 2A–B (**A**) Receiver operating characteristic (ROC) for Δ erythrocyte sedimentation rate and (**B**) ROC for Δ C-reactive protein is shown. The straight line indicates the demarcation below which is an area under the curve (AUC) of 0.5. Δ: value at resection − value at reimplantation.

Table 3. Positive cultures at time of reimplantation as assessed by AUC values

Variables	AUC	95% CI	p Value
ESR before reimplantation	0.594	0.413–0.797	0.29
CRP before reimplantation	0.627	0.481–0.758	0.21
ESR (Δ)	0.514	0.316–0.704	0.94
CRP (Δ)	0.353	0.196–0.528	0.09

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; AUC = area under the curve; CI = confidence interval; Δ = value at resection − value at reimplantation.

p = 0.778). The difference between the CRP at the time of reimplantation and resection showed poor discriminatory capacity with an AUC of 0.468 (CI, 0.327–0.608; p = 0.639). Similar results were obtained when using the second definition of persistent infection (positive cultures at the time of reimplantation) as end point with ESR and CRP values and their difference from resection registering too low of an AUC to be of clinical importance (Table 3).

Among the 34 patients who had arthrocentesis before reimplantation as a result of a high clinical suspicion of unrelenting infection, 33 had negative aspirates, but five of the 33 patients (15%) had positive intraoperative cultures at the time of reimplantation. One patient had a positive fluid culture that yielded MRSA. Treatment consisted of another round of 6 weeks of intravenous antibiotics. Intraoperative cultures at the time of reimplantation were negative, and the patient was infection-free at latest followup.

Discussion

The diagnosis of PJI relies on a combination of factors and diagnostic modalities, which include serologic markers such as CRP and ESR [2, 3, 19]. Although the value of ESR and CRP in diagnosing PJI is not disputed, the usefulness of these markers before reimplantation surgery remains unknown. A recent study by Greidanus et al. [9] using ROC techniques proposed cutoff values for ESR and CRP that can discriminate between infected and noninfected TKA. We are unaware of any study that applies similar fundamentals for patients undergoing the second-stage reimplantation procedure. Although we do not dispute the importance of using these markers to monitor progression of treatment, the strategy to defer reimplantation surgery until all serologic markers have returned to normal is not scientifically supported. The concern with reliance on normal serologic markers as the "green light" for reimplantation is that some patients may be subjected to a prolonged period of disability after resection arthroplasty and before reimplantation. There is equal concern with reimplanting a knee in which infection has not successfully been eradicated. Aspiration of the knee before reimplantation has been attempted as an alternative diagnostic modality to confirm the eradication of infection [15]. However, the high false-negative rates of culture possibly resulting from the intravenous antibiotic treatment have raised concerns. Thus, the question that arises is what factor(s) best predict successful eradication of infection in a patient with a previously resected knee.

Our study is not without some limitations. The 16 patients who underwent revision of their cement spacer block as a result of recurrence of infection before reimplantation may have biased the mean serologic levels. However, these patients underwent another round of 6 weeks of intravenous antibiotics. The ESR and CRP were then drawn on average 3 to 6 weeks after finishing the course of antibiotics similar to the majority of patients who did not have revision of their spacer. Three additional patients were delayed for at least 1 year as a result of medical issues that required optimization before reimplantation. Furthermore, the timeframe between the

reimplantation and resection procedures differed among patients because some were reimplanted later compared with others, which may have given the ESR and CRP time to taper off or return to normal. Our study may have been underpowered and a Type II error committed because of the relatively low rate of recurrence of PJI after reimplantation (21%), which could have masked the discriminatory capacity of ESR and CRP in detecting persistent infection. Another caveat that must be kept in mind is that only patients with a high clinical suspicion were aspirated before reimplantation, during which we may have missed cases with ongoing PJI.

Using ROC analysis, we could not determine a level for ESR or the CRP that could discriminate between patients in whom infection had successfully been eradicated versus those with persistent PJI. We calculated the difference between the ESR and CRP values before resection and reimplantation to remove the variability in baseline levels. Nonetheless, the change in serologic values proved to have the same poor discriminatory power as the absolute levels. Although the serologic tests were analyzed on average 2 to 3 months after resection, one may argue in favor of delaying reimplantation even further to improve the diagnostic accuracy of serology. This prospective study did not intend to interfere with the "standard of care" and hence did not institute changes in protocol. It is our institutional policy that reimplantation is usually performed within 2 to 4 weeks of completion of antibiotic treatment, allowing some outliers, as was the case in this study.

We were not surprised at the failure of ESR to emerge as a valuable marker predicting persistent infection because normalization of this marker may not occur for at least 3 months and up to 1 year postoperatively [1, 24]. Given that CRP is an acute phase reactant that elevates after surgery but normalizes in 2 to 4 weeks [17], we presumed it would have superior discriminatory capacity to ESR. The finding of the study in that CRP could not be reliably used to assess persistent infection was counterintuitive. Recently, Bottner et al. evaluated the role of interleukin 6 (IL-6), CRP, procalcitonin, and tumor necrosis factor-alpha (TNF-α) in distinguishing PJI from aseptic mechanical failure during preoperative workup [5]. They reported IL-6 and CRP measurement provide excellent screening tests for PJI. A highly specific marker such as procalcitonin or TNF-α and culture of the joint aspirate may be effective in confirming PJI in patients with positive CRP and/or IL-6 levels. Further research should be directed towards these new markers of PJI as potential indicators of persistent infection at time of reimplanting a TKA.

We also observed that aspiration of the knee could not be relied on to exclude infection either. False-negative aspiration was observed in 15% of cases in this cohort that compares similarly to that reported by Lonner et al. [15]. In the latter study, a false-negative rate of 25% was observed for knee aspiration in a group of 34 patients with infected TKA who were treated by two-stage exchange arthroplasty. The latter was despite delaying the aspiration for 2 to 3 weeks after stopping antibiotics. Antibiotic treatment before aspiration is a major cause of false-negative results [3]. Although arthrocentesis was performed an average of 4 to 6 weeks after stopping antibiotics, the aspirate detected persistent infection in only one of six patients.

Our prospective study highlights one critical point in that no single factor can be used alone in measuring the success of resection arthroplasty in eradicating infection. One should hence rely on a combination of clinical and laboratory factors to determine the timing of reimplantation. There appears to be little role for deferring reimplantation until all serologic markers have normalized. The latter can subject the patients to prolonged disability, overburden the resources, and potentially compromise the outcome of later reimplantation by causing soft tissue contractures and further bone loss. Influenced by the findings of this study, we currently proceed with reimplantation when four important prerequisites are in place. First, and perhaps the most important, is that a trend toward normalization and, in most cases, a return to normal CRP value should be observed and this trend needs to persist despite discontinuation of antibiotics; and second, the underlying cause of infection (if identified) is adequately addressed. Therefore, patients with recurrent urinary tract infection, cellulites, poor dentition, or skin ulceration should be investigated and all strategies for treatment and prevention of subsequent recurrence implemented. Third, optimization of immunocompromised, malnourished, and medically unwell patients should be implemented before reimplantation surgery. Finally, and based on clinical acumen, the knee is deemed ready for reimplantation with all soft tissues healed and erythema resolved.

Diagnosing PJI before reimplantation remains difficult given the poor diagnostic value of serology and aspiration before reimplantation. Nonetheless, a reinfection rate of 20% after reimplantation remains unacceptable, especially when they can be avoided. Hence, innovative diagnostic modalities that can detect lingering PJI with speed and accuracy are required to improve the efficacy of two-stage reimplantation for infected TKA.

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