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SYMPOSIUM: PERIPROSTHETIC JOINT INFECTION

What is the Role of Serological Testing Between Stages of Two-stage Reconstruction of the Infected Prosthetic Knee?

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Abstract

Background Two-stage exchange arthroplasty is the gold standard for treatment of infected TKA. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and synovial fluid white blood cell (WBC) count with differential are often used to determine treatment response; however, it is unclear whether these tests can answer the critical question of whether joint sepsis has been controlled between stages and if reimplantation is indicated.

Questions/purposes We therefore asked if (1) these serologies respond between stage one explantation and stage two reimplantation during two-stage knee reconstruction for infection; and (2) changes in the values of these serologies are predictive of resolution of joint infection.

Methods We retrospectively reviewed the serologies of 76 infected patients treated with a two-stage exchange protocol. The ESR, CRP, and aspiration were repeated a minimum of 2 weeks following antibiotic cessation and prior to second stage reoperation. Comparisons were made to identify trends in these serologies between the first and second stage procedures.

Results Eight knees (12%) were persistently infected at the time of second stage reoperation. The ESR remained persistently elevated in 37 knees (54%), and the CRP remained elevated in 14 knees (21%) where infection had been controlled. We were unable to identify an optimum cutoff value for the ESR, CRP, or the two combined. The best test for confirmation of infection control was the synovial fluid WBC count.

Conclusions Although the ESR, CRP, and synovial fluid WBC counts decreased in cases of infection control, these values frequently remained elevated. We were unable to identify any patterns in these tests indicative of persistent infection.

Level of Evidence Level II, diagnostic 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 approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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Introduction

One of the complications of TKA is deep periprosthetic infection. Chronic infections are typically treated in North America with a two-stage exchange protocol [4, 12, 17]. Despite the high success rate of a two-stage exchange for controlling infection, some patients will have persistent infections even with component removal, débridement of the joint, antibiotic spacer insertion, and treatment with systemic antibiotics [7, 8, 10].

Serum ESR and CRP, and synovial fluid WBC and differential of polymorphonuclear cells (%PMN) are commonly used for initially diagnosing an infected total knee arthroplasty. The literature is replete with studies that demonstrate the utility of these tests in the initial diagnosis of infection [1, 3, 14–16]. However, these studies do not address the important question of whether these same tests can be used to determine if infection has been controlled after the first stage resection arthroplasty and prior to the second stage reconstruction procedure. Little published data are available to indicate whether these tests can show joint sepsis has been controlled between stages and if reimplantation is indicated [6, 8, 15]. Second stage reimplantation in the setting of persistent infection can results in disastrous complications and the need for further resection arthroplasty and arthrodesis [12, 13, 17].

Therefore, we asked if (1) the ESR, CRP, synovial fluid WBC count with differential responds to treatment of infected TKA with a two-stage protocol; (2) these serologies respond differently in patients where infection is controlled versus those with persistent infection between stages; (3) receiver-operator curves (ROC) could be utilized to establish cutoff values for the ESR, CRP, and WBC count with differential to assist surgeons in deciding whether infection has been sufficiently controlled to allow reimplantation of a patient with a new total knee prosthesis, or whether continued treatment with an antibiotic spacer and systemic antibiotics is indicated; (4) we could generate area under the curve (AUC) data for each lab test to determine the diagnostic effectiveness of each lab test; (5) certain organisms correlated with higher rates of success or failure than others and false-positive or false-negative cultures were observed at the time of second stage reimplantation in groups where infection was controlled or persistent.

Patients and Materials

This study involved a retrospective review of chart data for 76 patients treated at two hospitals for a deep periprosthetic infection of a TKA using an identical two-stage exchange protocol. The mean age of the patients at the time of first stage explant was 65.5 years-old (range, 43–83 years). Thirty-four (45%) patients were men and 42 were women (55%). The mean interval between the first stage explant and proposed second stage reimplantation was 74 days (range, 56–203 days). Of the 76 patients, 68 (89.5%) achieved infection control, while eight (10.5%) patients remained persistently infected. The mean ESR of patients at the time of initial diagnosis was 59.9 (range, 10–140). The mean CRP was 36.8 (range, 1–267.8), while the mean synovial fluid WBC count was 57974 (range, 1000–846,000). The mean percentage of PMNs in the synovial fluid was 90.2 (range, 50–100). The commonly accepted cutoffs of 30 mm/hr for ESR, 10 mg/L for CRP, 3,000 WBC/μl for the synovial fluid WBC count, and 80% PMN for differential were used as reference or normal values for these tests [3].

All surgery was performed by two surgeons (SMS and CDV). For the purposes of this study, "stage one" is defined as the initial surgical procedure, or resection arthroplasty, during which a newly diagnosed patient underwent prosthetic component removal along with extrication of any associated cement, followed by placement of an antibiotic loaded spacer, containing four grams of vancomycin and 3.6 grams of tobramycin per 40 grams of cement. This was consistent across patients.

After this stage one procedure, patients received 6 weeks of organism specific intravenous antibiotics. The ESR and CRP were then repeated no less than 2 weeks after antibiotic cessation. Additionally, a repeat aspiration of the knee was performed at this time and this fluid was sent for aerobic, anaerobic, and fungal cultures along with a synovial fluid WBC count with differential.

Patients then underwent a "stage two" surgical procedure, which was defined as the second stage reconstruction procedure. During this stage two procedure, the surgical procedure involved planned removal of the antibiotic spacer followed by placement of new knee arthroplasty components. Additionally at this time, three sets of intraoperative cultures were obtained, and synovial tissues were sent for intraoperative frozen sections and permanent histopathology. If at this time patients had evidence of persistent infection, joint reconstruction was aborted and a repeat débridement and spacer placement was performed.

Patients were considered persistently infected at stage two if they had two positive cultures, or they met two of the three following criteria: (1) at least one positive culture; (2) histopathology consistent with infection (an average of at least 10 polymorphonuclear (PMN) cells in the five most cellular fields); and/or (3) grossly infected tissues seen at the time of reoperation [1, 4, 10]. Patients were considered to have false positive cultures at stage two if they did not, meet the above criteria. Therefore, patients with only one positive culture, or patients who only met one of the above three criteria were considered to have false positive cultures at stage two.

To answer the first two questions of our analysis, we used a paired t-test to compare laboratory values obtained prior to stage one to those obtained at the time of the stage two procedure. We also used this same statistical analysis to compare lab values between those patients where infection was controlled and where it was persistent. To answer our third question, we used a one-way analysis of variance test to compare the lab values of patients who

achieved infection control versus those who did not. We then generated ROCs to determine optimal cut-off values for each lab test, and also to determine if any one or combination of tests could reliably identify persistent infection. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each test at the optimum cutoff point were also determined. To answer our fourth question, area under the curve data (AUC) for each ROC curve was determined as a measure of diagnostic effectiveness of each assay. An AUC of 0.5 for a given lab test indicates that for a given calculated cutoff value, a test has a 50% chance of correctly classifying a patient into the infected or uninfected category. As the AUC for a particular lab test increases, the accuracy of that test for diagnosing infection also increases. Finally, to answer our fifth question, we analyzed the culture data by organism speciation and also by the group in which infection was controlled versus the group in which infection persisted. All statistical tests were performed using SPSS version 14 (SPSS Inc., Chicago, IL) with significance set at alpha = 0.05.

Results

Comparison of the mean ESR, CRP, synovial fluid WBC, and differential between stages for all patients demonstrated declines in all lab values (Table 1). Of the 76 total patients, 68 (89%) achieved infection control with the two-stage protocol, while eight (11%) remained persistently infected. Species identification of the infection control group and the persistent infection group demonstrated a high percentage of Staphylococcus species in both groups (Table 2). The persistently infected group had a very high percentage of methicillin resistant Staphylococcus species.

Comparisons of the mean lab values after stage one for patients with controlled infection versus those with persistent infection showed no differences for all four lab values measured (Table 3). The mean CRP after stage one was actually LOWER in the persistently infected group compared to the infection control group (Table 3).

Table 1. Changes between stages for all subjects (n = 76)

Test result	Stage 1	Stage 2	p Value
Mean ESR (mm/hr)	59.9 (10–140)	37.4 (1–140)	< 0.001
Mean CRP (mg/L)	36.8 (1–267.8)	6.1 (0.2–46.3)	< 0.001
Mean synovial fluid WBC count (per μl)	57,974.0 (1000–846,000)	1,864.5 (75–16,000)	< 0.001
Mean % PMN	90.2 (50–100)	58.3 (7–95)	< 0.001

Analysis of the patients who achieved infection control revealed decreases in the values of all four variables between stages (Table 4). Based on the accepted cutoffs described earlier, the ESR returned to normal in only 46% of these patients, while the CRP normalized in 79%. Both the CRP and ESR returned to normal in only 37%. The synovial fluid WBC returned to normal in 80% of this group, while the differential normalized in 66%. The WBC and differential both returned to normal in only 37%.

Conversely, analysis of those eight patients with persistent infection demonstrated no significant reductions in these four lab values between stages (Table 5). Utilizing

Table 2. Bacterial species of controlled infection versus persistent infection groups

Bacterial species	Controlled	Persistent
MRSA	7 (10.3%)	2 (25%)
MRSE	13 (19.1%)	3 (37.5%)
MSSA	13 (19.1%)	2 (25%)
MSSE	11 (16.2%)	1 (13.5%)
E. coli	1 (1.5%)	
Enterobacter cloacae	1 (1.5%)	
Pseudomonas	2 (2.9%)	
Streptococcus spp.	3 (4.4%)	
VRE	1 (1.5%)	
VSE	1 (1.5%)	
No growth	15 (22.1%)	
Totals	68	8

Table 3. Stage 2 means by group (controlled infection versus persistent infection)

Test result	Controlled (n = 68)	Persistent (n = 8)	p Value
Mean ESR (mm/hr)	36.8 (1–140)	43.5 (18–75)	0.56
Mean CRP (mg/L)	6.3 (0.2–46.3)	4.1 (0.4–18.4)	0.56
Mean synovial fluid WBC count (per μl)	1,778.3 (75–16,000)	3,243.8 (360–8100)	0.32
Mean % PMN	57.7 (7–95)	68.3 (31–87)	0.39

Table 4. Laboratory values in controlled infection group (n = 68)

Test result	Stage 1	Stage 2	p Value
Mean ESR (mm/hr)	61 (10–140)	37.2 (1–140)	.0001
Mean CRP (mg/L)	40.14 (1–267.8)	6.25 (0.2–46.3)	.0001
Mean synovial fluid WBC count (per μl)	57313 (1000–846,000)	1688 (75–16,000)	.0002
Mean % PMN's	89.8 (50–100)	57.8 (7–95)	.0001

Table 5. Persistent infection means by stage (n = 8)

Test result	Stage 1	Stage 2	p Value
Mean ESR (mm/hr)	52.0 (26–78)	43.5 (18–75)	0.4
Mean CRP (mg/L)	11.4 (1.5–32.3)	4.1 (0.4–18.4)	0.1
Mean synovial fluid WBC count (per μl)	86,850.0 (8300–154,250)	3,243.8 (360–8100)	0.2
Mean % PMN	94.7 (92–98)	68.3 (31–87)	0.1

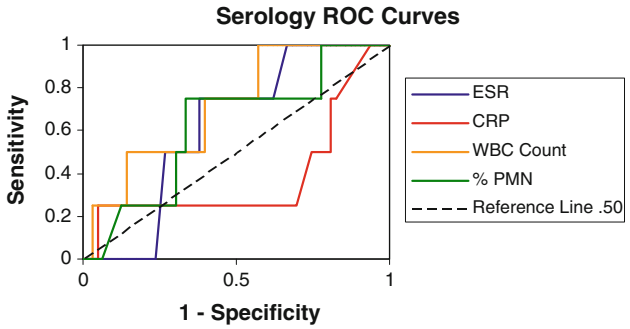

Fig. 1 A chart shows the receiver-operator curves for selected variables. Reliability of a test increases as area under the curve (AUC) increases. An AUC equal to 0.5 indicates a 50% probability of detecting infection. Examination of the plot shows the ESR, WBC count, and % PMN are somewhat more reliable than 0.5, whereas CRP is actually less reliable (Table 6).

Table 6. Cutoffs and predictive values

Value	ESR (mm/hr)	CRP (mg/L)	Synovial fluid WBC count (per μl)	% PMN
Optimum cutoff	43.5	17.75	1102.5	71.5
Sensitivity	0.67	0.17	0.75	0.75
Specificity	0.62	0.94	0.61	0.66
PPV	0.13	0.20	0.11	0.12
NPV	0.05	0.07	0.03	0.02
Accuracy	0.62	0.88	0.62	0.66
Area Under Curve	0.62	0.39	0.71	0.62

the cutoff values described above, the ESR returned to normal in 38% while the CRP normalized in 88%. Both were persistently elevated in only one (12%) patient. The synovial fluid WBC count normalized in 50% of this group, while the differential returned to normal in 63%. In no case did both values remain persistently elevated.

The ROCs generated for the four lab values we analyzed had low AUC values (Fig. 1, Table 6). The optimum cutoff values that we calculated resulted in low values of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (Table 6). None of the four tests were independently acceptable predictors of persistent infection. Combining lab tests also did not improve the ability to diagnose persistent infection. The synovial WBC count had the highest AUC of all four tests (0.71) but still did not have sufficient accuracy, sensitivity, or positive predictive value to reliably diagnose persistent infection (Table 6).

Finally, analysis of culture data demonstrated that of the 68 patients in whom infection was controlled, six patients had positive cultures at reaspiration after stage one. These were all judged to be false positive cultures based on the criteria described above. The organism isolated from all of these false positive cases was S. epidermidis. None of these patients were infected with this organism at the time of initial infection diagnosis.

Of the eight persistently infected patients, five patients had negative cultures at reaspiration. However, all five of these patients fulfilled the other criteria for infection described above. In the three patients that did have persistently positive cultures, the organism at time of reoperation was the same as the initially cultured in two patients, and was different in the third.

Discussion

Deep periprosthetic infection continues to occur after TKA. Although two-stage exchange has a high success rate for controlling sepsis, infection can persist despite this treatment [7, 8, 10]. Identification of persistent infection following resection arthroplasty is absolutely critical for obtaining optimal results [12, 13]. Although the literature is replete with studies that demonstrate the utility of the ESR, CRP, synovial fluid WBC, and differential of polymorphonuclear cells (%PMN) for initially diagnosing infected TKA, very few studies exist that demonstrate whether these same tests can be used to determine if infection has been controlled after the first stage resection arthroplasty and prior to the second stage reconstruction procedure [1, 15, 16] (Table 7). No previous studies have documented the trends in all four of these lab values from stage one to stage two in patients who have undergone two-stage exchange for infected total knee arthroplasty.

Our study is subject to several limitations. First is the small number of persistent infections at the time of reimplantation. This limits the power of the study and may skew certain predictive values such as false negatives and accuracy. However, all studies in the literature that address this particular topic are hampered by similar statistical power issues. Second, although we strove to use accepted definitions for persistent infection that have been used in similar studies, there is no set of definitive criteria for

Table 7. Comparative literature on perioperative serology testing for prosthetic joint infection

Authors	Initial CRP (mg/L) (before stage 1)	Initial ESR (mm/h) (before stage 1)	Initial WBC count (before stage 1)	Initial % PMNs in joint fluid (before stage 1)	CRP (mg/L) between stage 1 and 2	ESR (mm/h) between stage 1 and 1	WBC count between stage 1 and 2	% PMNs between stage 1 and 2
Austin et al. [1]	110	85	N/A	N/A	N/A	N/A	N/A	N/A
Della Valle et al. [3]	123	79.6	56,573	92	N/A	N/A	N/A	N/A
Ghanem et al. [6]	N/A	N/A	N/A	N/A	2.13	49	N/A	N/A
Schinsksy et al. [14]	52.4	55.4	61,336	86.1	N/A	N/A	N/A	N/A
Kusuma et al. [current study]	36.8	59.9	57,974	90.2	6.1	37.4	1864.5	58.3

infection. Therefore, it is possible that some patients may have been miscategorized as persistently infected or not infected [3, 6]. Again, the literature is replete with studies that demonstrate the extreme difficulty of identifying true infection control or persistence. Finally, as with any with any study that examines the topic of persistent infection, there are a large numbers of variables from one patient to the next, particularly with regard to medical comorbidities and other systemic conditions that can affect the CRP and ESR values. However, despite these weaknesses, our study does document the extreme difficulty of determining infection control versus persistence during two-stage treatment.

With regard to our first two study questions, our data do clearly demonstrate these four lab values decline precipitously after stage one resection arthroplasty regardless of infection control or persistence, and also that these declines are substantial when infection is controlled. Unfortunately comparisons between the infection controlled and persistently infected groups revealed no differences in these variables that could help guide treatment. One explanation for this is we had a very small number of patients who were persistently infected. The ability to compare to a larger group of persistently infected patients would allow for better statistical comparisons. Additionally, the inflammatory response in patients with persistent infection was neither robust enough to generate large increases in the local and systemic markers of infection at the time of initial infection, nor to control the infection after resection arthroplasty. Very few other studies have accurately documented the trends in these four lab values between stage one and stage two of infected TKA treatment [6]. Ghanem et al. also demonstrated that these lab values decrease between stages but that no differences between infection controlled and persistently infected groups could be found [6].

The complexity of these data highlights the difficulty of determining persistent infection following recent surgery. While it is common practice for surgeons to wait until the ESR and CRP have "normalized" prior to attempted reimplantation, our data and those of others show this practice will not be reliable [6, 8]. The combination of the normal inflammatory response from surgery, antibiotics in the cement spacer, and recent systemic antibiotic administration likely affect these systemic variables in multiple ways, resulting in erratic and unpredictable values.

Other authors have proposed obtaining repeat cultures after antibiotic cessation and prior to stage two reimplantation to determine whether persistent infection is still present [13]. However, routine use of this practice has not been recommended as repeat cultures are fraught with sampling errors and high false negative rates and poor sensitivity [9, 11]. Thus, no good tests are currently

available to accurately determine persistent prosthetic joint infection after stage one resection.

With regard to our third and fourth study questions, again we were unfortunately unable to define useful ROCs or AUC values that would yield cutoff lab values that allow accurate determination of whether infection was controlled or not. Of the variables examined, the synovial WBC count at the time of reimplantation had the highest AUC (0.71) and was the best perioperative test prior to stage two reimplantation. Other authors suggest synovial fluid WBC count accurately detects infected versus uninfected knees prior to revision TKA [3, 16]. This finding indicates the systemic response to the treatment of infected TKA is more variable than the local intraarticular response. The ESR and CRP are of course systemic parameters of infection and showed high variability between stages and between controlled infection and persistently infected groups, and while these tests have been reliable at initially diagnosing periprosthetic joint infection, they are not reliable for diagnosing persistent infection between stages of two-stage treatment [6, 15]. Again, the study of Ghanem et al. is the only other in the current literature that addresses the particular issue of serologic tests between stages of two-stage exchange treatment [6]. These authors were similarly unsuccessful in attempts to produce ROC and AUC data for these lab values that would reliably predict infection control or persistence.

With regard to our final question, we also examined the utility of culturing the joint fluid prior to reimplantation and found a high incidence of both false positive and false negative results. This is similar to Lonner et al., who demonstrated the microbiological analysis of reaspiration fluid of infected TKA between stages was not useful in identifying persistent infection, as there was a high prevalence of false negative cultures in this setting [11]. Conversely, Mont et al. demonstrated in the setting of two-stage reimplantation of infected knees, aspiration and culture of synovial fluid prior to planned second stage reimplantation was a useful step in reducing the incidence of recurrent infection after second stage reimplantation [13]. They showed a reduced rate of recurrent infection after second stage reimplantation by repeat débridement of those patients who had persistently positive cultures prior to the planned second stage reconstruction. Again, these conflicting reports highlight the extreme difficulty of diagnosing recurrent infection prior to second stage reimplantation. However, we still advocate diligent use of aspiration and cultures prior to second stage reimplantation in all patients.

We were unable to identify any single, or combination of, commonly used testing modalities to reliably identify persistent infection following resection TKA for a deep periprosthetic infection. The ESR and CRP were particularly unreliable and frequently abnormal even when infection had been controlled. New and novel testing modalities may be required to further identify persistent infection in this setting prior to reimplantation. Ultimately, if the ESR and CRP are still elevated and nondiagnostic at the time of planned second stage reimplantation surgery, we will proceed with reimplantation if the tissues appear noninfected, if the intraoperative frozen sections are consistent with control of infection, and if the WBC of the aspirate fluid is less than 3,000 WBC/μl and the differential is less than 80% PMN [3, 6]. If these values are not consistent with control of infection, we will proceed with a second débridement and repeat cement spacer insertion.

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