Clin Orthop Relat Res (2008) 466:2628–2633
DOI 10.1007/s11999-008-0471-5

SYMPOSIUM: PAPERS PRESENTED AT THE ANNUAL MEETINGS OF THE KNEE SOCIETY

Diagnosis of Infected Total Knee

Findings of a Multicenter Database

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Published online: 10 September 2008

Abstract Although total knee arthroplasty (TKA) is an effective and successful procedure, the outcome is occasionally compromised by complications including periprosthetic joint infection (PJI). Accurate and early diagnosis is the first step in effectively managing patients with PJI. At the present time, diagnosis remains dependent on clinical judgment and reliance on standard clinical tests including serologic tests, analysis of aspirated joint fluid, and interpretation of intraoperative tissue and fluid test results. Although reports regarding sensitivity and specificity of all diagnostic tests in the literature are abundant, the interpretation of the available data has been hampered by the low sample size of these studies. In view of the scope of this important problem and the limitations of previous reports, a large database was assembled of all revision TKA performed at three academic referral centers in order to determine the current status of diagnosis of the infected TKA utilizing commonly available tests. Intraoperative cultures should not be used as a gold standard for PJI owing to high percentages of false-negative and false-positive cases. When combined with clinical judgment, total white cell count and percentage of neutrophils in the synovial fluid more accurately reflects PJI and when combined with hematologic exams safely excludes or confirms infection.

Level of Evidence: Level II, prognostic 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 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

Total knee arthroplasty (TKA) is performed in the United States on over 400,000 patients annually with the number of procedures projected to double within 10 years [5, 14]. Though effective and successful, the outcome of TKA is occasionally compromised by complications [3, 9, 10, 19]. Periprosthetic joint infection (PJI) is one such complication that occurs after 1% to 3% of TKA translating to around 10,000 cases per year in the United States [8, 18].

It appears that despite all efforts for prevention, PJI will continue to pose challenges to the orthopaedic community. One of the problems associated with PJI relates to timely diagnosis of this complication [4, 16]. Accurate and early diagnosis is the first step in effectively managing patients with PJI [7, 8]. At the present time diagnosis remains dependent on clinical judgment and reliance on standard clinical tests including serologic tests such as sedimentation rate (ESR), C-reactive protein (CRP), white blood cell

count (WBC), analysis of aspirated joint fluid, and interpretation of intraoperative tissue and fluid test results. Typically the diagnosis will be based on a combination of findings, rather than a single one [1, 20].

However, PJI may occasionally escape diagnosis because of a multitude of reasons. First, the clinical presentation of PJI can be innocuous and mimic other conditions. Second, the radiographic workup in the diagnosis of PJI is rarely informative and cannot distinguish between septic and aseptic failures. More importantly, there is no single test with absolute accuracy for diagnosis of PJI. Although reports regarding sensitivity and specify of numerous diagnostic tests in the literature abound, the interpretation of the available data has been hampered by the low sample size of these studies. One such example is the analysis of synovial fluid for leukocyte count and neutrophil percentage; a high sensitivity of 94% and 97% and a specificity of 88% and 98% respectively have been reported [21]. However, the cutoff values for the fluid cell count and neutrophil differential [11, 16] are not agreed upon.

We conceived our investigation to confirm current concepts in the diagnosis of PJI and introduce new ones based on data available from multiple joint arthroplasty centers. Our goal was to investigate the role and efficacy of serological tests and synovial fluid analysis during the preoperative evaluation of patients with suspected PJI. Based on past literature we presumed combining tests can lead to superior diagnostic value in terms of sensitivity, specificity, and predictive value [7, 15, 16]. We believed the efficacy of Gram stain in diagnosing PJI intraoperatively can be improved by analyzing both the number of stained white blood cells and looking for the presence of organisms. Although intraoperative culture has been deemed as the gold standard for diagnosing PJI, some investigators have challenged this notion [2, 4, 6, 8]. A review of our pooled data was performed to determine the false negative incidence of intraoperative culture, and the role that prophylactic antibiotics given prior to revision surgery may have on culture results. Finally, we explored the clinical fate of patients with a false positive unexpected intraoperative culture.

Materials and Methods

We assembled a single database comprised of detailed data on all patients undergoing revision TKA for all reasons in three academic centers from 2000 to 2005. There were a total of 889 patients in this cohort with a mean age of 67 years (range, 43–94 years). Patients were diagnosed with periprosthetic infection if they fulfilled one of the following criteria: (1) an abscess or sinus tract was found 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 intracapsular purulence or abnormal histology [12]. Intraoperative culture results were classified as false positives if a single positive culture occurred in the absence of other signs of infection described above. Of the 889 patients 197 (22%) met one of these criteria. The incidence of PJI was similar among the three institutions. Data routinely collected on this cohort included prophylactic antibiotic administration; preoperative ESR, CRP, and WBC; analysis of aspirated joint fluid (when performed) for absolute cell count; percentage of neutrophils; gram stain and culture; and analysis of intraoperative gram stain and culture results.

We identified the 171 TKA patients from the 197 with an infection who had a positive preoperative joint aspiration culture. We documented the details of any antibiotics given preoperatively. The result of intraoperative culture samples was then correlated with the preoperative joint aspiration findings to determine the false negative rate. We further determined the influence of administration of prophylactic antibiotics on isolation of an organism(s) from the intraoperative cultures.

We identified 296 total knee revisions performed at one of the participating institutions from the total of 889 patients revised who had both an ESR and CRP drawn as part of the preoperative workup. The serology tests from a single institution were included in order to prevent a confounding variable that may have been introduced by including lab values from different institutions. The sensitivity, specificity, and predictive values were calculated for each test alone and when combined together. The cost of the serological tests was compared to that of other preoperative diagnostic modalities including Indium scans, FDG-PET imaging, and joint fluid analysis.

We defined a positive gram stain as the visualization of bacterial cells or “many leukocytes” (> 5 per high-power field) under the smear. The sensitivity, specificity, and predictive values of visualizing bacterial cells or stained white cells in diagnosing PJI according to these criteria were determined separately and in combination. One set of combinations performed required both bacteria and “many leukocytes” to be positive to confirm infection. The second set of combinations required both bacteria to be absent and < 5 leukocytes per high-power field were visualized to be negative to rule out infection.

To define cutoff values for fluid leukocyte count and neutrophil percentage we used synovial fluid analysis performed on 429 TKA (161 infected; 268 aseptic) at the three institutions. The sensitivity, specificity, and predictive values were calculated for the above cutoff values

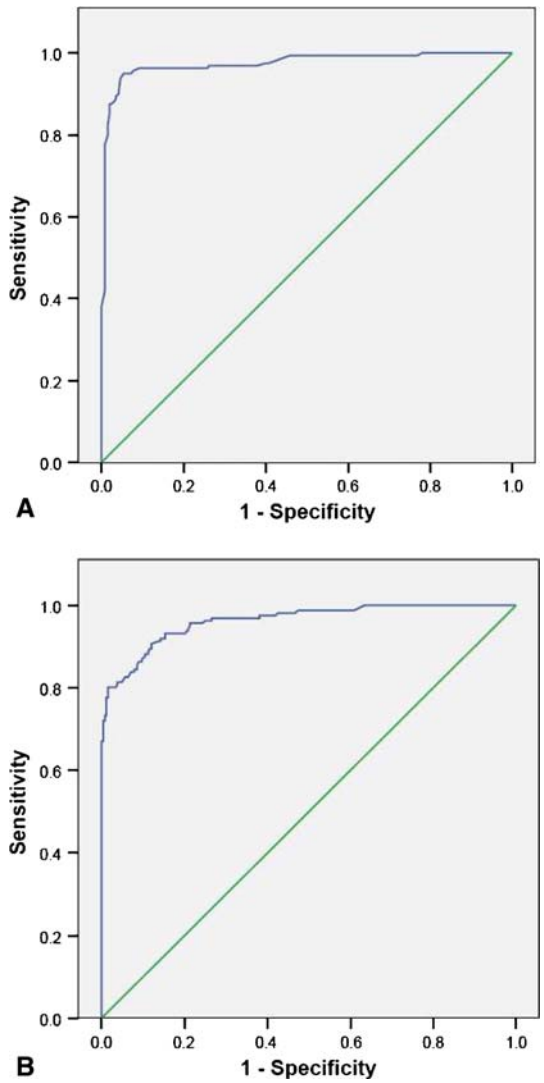

Fig. 1A–B Receiver operating curves for predicting periprosthetic infection are illustrated. An area under the curve of 1 demonstrates an ideal test with a 100% sensitivity and specificity, while an area under the curve less than 0.5 indicates that the diagnostic has poor discriminatory value. (**A**) The cutoff value for optimal accuracy in diagnosis of PJI was 1100 cells/μL for fluid leukocyte count. (**B**) The cutoff value for optimal accuracy for fluid neutrophil differential was 64%. When both tests yielded results below their cutoff values, the negative predictive value of the combination increased to 99.6%, while if both tests were greater than their cutoff values the positive predictive value improved to 100%.

using receiver operating curves. The ESR and CRP cutoff values of 30 mm/hr and 10 mg/L respectively were combined with the above determined cutoff values for fluid leukocyte count and neutrophil percentage to improve the diagnostic value of each test when used separately.

To assess the accuracy of intraoperative cultures in isolating an infecting organism, the rate of false-negative and false-positive intraoperative culture was determined. False negative was defined as the absence of isolation of any organisms from intraoperative samples in patients with "proven" PJI based on a positive preoperative aspirate, elevated serology, and/or elevated cell count/differential. False positives were determined based on the isolation of organisms from intraoperative culture samples in patients who did not exhibit signs of infection for at least 2 years following revision TKA, despite receiving no treatment for infection.

The estimated sensitivity, specificity, predictive values, and likelihood ratios were calculated for the different preoperative and intraoperative variables, and the 95% confidence intervals (CI) were reported. A p value of < 0.05 (two-sided) was considered significant. All analyses were performed using SPSS, version 13 (SPSS, Inc., Chicago, IL). Receiver operating characteristic (ROC) curves which depict the relation between true-positive (sensitivity) and false-negative (1-specificity) cases were constructed for the fluid leukocyte count and neutrophil percentage (Fig. 1A–B). The area under the curve was calculated for each of the above variables and compared. An area under the curve of 1 demonstrates an ideal test with a 100% sensitivity and specificity, while an area under the curve less than 0.5 indicates that the diagnostic test is less useful. The cut-off values of fluid leukocyte count and neutrophil percentage for optimal diagnosis of PJI were determined. The sensitivity, specificity, and predictive values were calculated for each of the cutoff values. We performed a pair-wise comparison of the area under the curve for the fluid leukocyte count and neutrophil percentage to determine which diagnostic test is best suited for diagnosing PJI.

Results

Of the 296 patients with preoperative ESR and CRP performed at one of the participating institutions, 116 patients (39%) were classified as infected and 180 patients (61%) were considered noninfected. The mean ESR and CRP of the infected patients at 85 mm/hr and 110 mg/L were higher ($p < 0.001$) than the corresponding values at 22 mm/hr and 7 mg/L for the noninfected knees. Five patients (4%) in the infected group had a normal ESR (< 20 mm/hr) and CRP (< 10 mg/L). Infection was suspected in all five patients and an organism was cultured on solid media in four of the five cases.

The evaluation of the joint aspirate from 429 TKA (161 infected; 268 aseptic) using receiver operating curves revealed that the cutoff values for optimal accuracy in diagnosis of PJI were 1100 cells/μL for fluid leukocyte count and 64% for neutrophil differential. When both tests yielded results below their cutoff values, the negative predictive value of the combination increased to 99.6%, while if both tests were greater than their cutoff values the

positive predictive value improved to 100%. Similarly, when both the neutrophil percentage and CRP were less than 64% and 10 mg/L respectively one can rule out PJI in the majority of cases.

The analysis of tissue cultures in 453 TKA patients revealed that the presence of organisms and "many" neutrophils on a gram smear had high specificity (98%–100%) and positive predictive value (89%–100%). However, the sensitivities (30%–50%) and negative predictive values (70%–79%) of the two tests were low. When the two tests were combined in series the specificity and positive predictive value were absolute (100%) with slightly improved sensitivity (43%–64%) and negative predictive value (82%).

Analysis of the results of intraoperative cultures revealed that there was a 10% incidence of false negative rate in patients with strong clinical suspicion for infection. This was despite the presence of gross pus in some of the cases. On the other hand, of a consecutive series of 692 revision TKAs, intraoperative cultures were unexpectedly positive in 41 cases (5.9%). Of these 41, 29 cases had a single positive intraoperative culture and were judged a probable false positive based on absence of any other evidence of infection, of which five were treated with an extended course of intravenous antibiotics after hospital discharge and the remaining 24 received no further treatment. None of these 29 patients manifested any sign of infection at a minimum followup of 24 months (average, 46 months; range, 24–74 months). Twelve patients were determined to have probable acute periprosthetic infection, 11 of whom were treated with a course of antibiotics. Two of these patients became reinfected within 1 year. The remaining 10 patients had no further sequelae.

Among the cohort of 171 patients with positive preoperative aspirate, 72 patients received prophylactic antibiotics within one hour of revision TKA. Intraoperative culture was negative in nine of 72 patients who received antibiotics corresponding to a false-negative rate of 12.5%. In contrast, an organism could not be isolated from intraoperative samples in eight of 99 patients who did not receive prophylactic antibiotics, corresponding to a false-negative rate of 8%. We found no difference ($p = 0.34$) in the incidence of false-negative cultures between those who did and those who did not receive perioperative antibiotics. In over 90% of cases administering antibiotics did not change the ability to detect a pathogen. A new organism was rarely discovered and when it was, it rarely had an impact on treatment.

Discussion

Periprosthetic joint infection has ascended to the highest rank as the cause of failure following joint arthroplasty [23]. Further, one study suggests a large number of what was once thought aseptic loosening may actually be due to undiagnosed infection and thus the rate of PJI might be an underestimate of the actual cases of infection [22]. Some studies suggest combining the results of several tests will yield a more accurate diagnosis of infection. Based on that literature we presumed combining tests can lead to superior sensitivity, specificity, and predictive value.

Although our study population included patients from multiple referral centers and is the largest cohort to date, we recognize some limitations. Because of the involvement of multiple centers some variability in data collection and analysis may have existed that could confound these findings. There may have also been differences among institutions with regard to interpretation of histological findings, Gram stain, and cell counts that could have also influenced the results. In order to minimize the variability we ensured that the same standardized units were used when examining laboratory tests such as the ESR, CRP, and cell counts. This study is also on patients undergoing revision TKA and its findings could not and should not be generalized to other joints. In addition, the analyses excluded patients with inflammatory arthropathy including rheumatoid arthritis, systemic lupus erythematosus, and gout because of their inherently elevated levels of fluid cell count, neutrophil percentage, and serological values. However, these limitations do not detract from our conclusions given that our large patient population affords us adequate power to reach deductions that reflect those present in the literature.

Periprosthetic joint infection, besides its psychological and financial burden on the patient and society, poses a major diagnostic challenge to the orthopaedic community [4]. Despite availability of various diagnostic modalities, confirmation of PJI can be difficult in some patients [6, 13, 15, 20]. Further, there is no consensus as to what constitutes a PJI, making its diagnosis very challenging [17]. Although literature abounds with reports on the accuracy of various tests for diagnosis of PJI [8, 13, 15, 16, 20], the small sample size and the conflicting findings of studies hinder the interpretation of the available data.

This multicenter study amassing a relatively large population of patients with and without PJI demonstrated some important findings. Perhaps one of the most important findings of the study was that administration of prophylactic antibiotic did not seem to interfere with isolation of an infecting organism. Infecting organisms could still be isolated from the intraoperative culture of over 90% of patients who received preoperative antibiotics. The incidence of negative cultures was not different between patients who received antibiotics versus those who did not. Thus the beneficial effect of prophylactic antibiotics should not be withheld from patients undergoing revision TKA. This is

particularly important as TKA is often performed under tourniquet and a delay in administration of antibiotic until tissue culture samples are obtained is more concerning. One important caveat of this study should be remembered: the findings of the study only apply to patients in whom an infecting organism has been isolated preoperatively.

Our data suggest intraoperative cultures cannot and should not be used as gold standards for diagnosis of PJI as there is a relatively high percentage of both false-negative and false-positive cases. Although the latter point has been expressed by several studies [2, 16, 20], others continue to advocate intraoperative cultures as the single most important test [8, 20]. We interpret our data as suggesting the joint aspirate fluid, with respect to total white cell count and percentage of neutrophils, is more accurate for diagnosis of infected TKA than intraoperative cultures. Again this was the case when a definite cutoff value for total cell count and the neutrophil percentage using receiver operating curve analysis had been performed and the cell analysis findings were combined with ESR and CRP values. Although Trampuz et al. [21] were the first to report cutoff values for fluid cell count and differential, they did not suggest the clinical importance of a situation when both tests reveal a positive or negative result. Spangehl et al. [20] also reported improved sensitivity, specificity, and predictive value when combining the test values of ESR and CRP. However, there is little data in the literature describing the combination of serological tests with aspiration fluid cell count or neutrophil differential. We found the clinical utility of fluid analysis in diagnosing infection can be improved by combining this test with serology findings. Combinations of cell count and differential and serology safely excluded or confirmed the presence of infection during the preoperative assessment of the patients with failed knees.

Our data also demonstrated that simple serological tests, namely ESR and CRP, are excellent screening tools and we believe they should be obtained in every patient with a painful TKA. Elevated ESR and/or CRP were highly predictive of PJI and should prompt further evaluation such as joint aspiration. This study could not evaluate the role of preoperative bone scan as an insufficient number of these tests had been performed in the cohort. The study, however, revealed that intraoperative gram stain and cell count carried a low sensitivity and negative predictive value. The latter tests should therefore not be used as screening tools. However, these fast and simple intraoperative test have a valuable role in reaching a diagnosis for ambiguous cases [4, 16].

Accurate and early diagnosis is the first step in effectively managing patients with PJI. At the present time, diagnosis remains dependent on clinical judgment and reliance on standard clinical tests including serologic tests, analysis of aspirated joint fluid, and interpretation of intraoperative tissue and fluid test results. In view of the scope of this important problem and the limitations of previous reports, we have determined the current status of diagnosis of the infected TKA utilizing commonly available tests.

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