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Two-stage Exchange Knee Arthroplasty

Does Resistance of the Infecting Organism Influence the Outcome?

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Abstract

Background Periprosthetic joint infection after TKA is a challenging complication. Two-stage exchange arthroplasty is the accepted standard of care, but reported failure rates are increasing. It has been suggested this is due to the increased prevalence of methicillin-resistant infections.

Questions/purposes We asked the following questions: (1) What is the reinfection rate after two-stage exchange arthroplasty? (2) Which risk factors predict failure? (3) Which variables are associated with acquiring a resistant organism periprosthetic joint infection?

Methods This was a case-control study of 102 patients with infected TKA who underwent a two-stage exchange arthroplasty. Ninety-six patients were followed for a minimum of 2 years (mean, 34.5 months; range, 24–90.1 months). Cases were defined as failures of two-stage exchange arthroplasty.

Results Two-stage exchange arthroplasty was successful in controlling the infection in 70 patients (73%). Patients who failed two-stage exchange arthroplasty were 3.37 times more likely to have been originally infected with a methicillin-resistant organism. Older age, higher body mass index, and history of thyroid disease were predisposing factors to infection with a methicillin-resistant organism.

Conclusions Innovative interventions are needed to improve the effectiveness of two-stage exchange arthroplasty for TKA infection with a methicillin-resistant organism as current treatment protocols may not be adequate for control of these virulent pathogens.

Level of Evidence Level IV, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

The incidence of periprosthetic joint infection (PJI) after TKA is approximately 2% [2, 14]. A variety of treatment protocols are used in managing this devastating complication. Two-stage exchange arthroplasty was originally described by Insall et al. [10] and has been widely adopted as the standard of care with reported success rates ranging from 80% to 95% [4, 10, 20, 25, 26].

However, there has been a marked rise in the incidence, 15–20% in the 1990s to 36–46% more recently, of PJI with resistant organisms, methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis (MRSE) [11, 12, 18, 23]. This is concerning to the orthopaedic community as multiple studies have reported lower success rates (18–76%) in treating resistant organism PJI [6, 8, 12, 16]. However, it is unclear whether the increased failure rate after two-stage exchange arthroplasty is associated with the virulence of the infecting organism. Furthermore, it is unclear which if any risk factors are associated with acquiring these resistant organism infections. Knowing which patients are at risk would help patients in making informed decisions about

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their healthcare, help physicians in appropriate patient selection, and through further research might allow tailored protocols for these patients.

We therefore asked the following questions: (1) What is the reinfection rate after two-stage exchange arthroplasty? (2) Which risk factors predict failure of the two-stage exchange arthroplasty procedure? And (3) which variables predispose our patient population to infection with a methicillin-resistant organism?

Patients and Methods

Our study cohort was generated by querying our computerized, prospective joint arthroplasty database between January 1998 and August 2005 for patients who had undergone a two-stage exchange arthroplasty procedure for the treatment of a PJI. PJI was defined by at least one of the following: positive preoperative aspiration cultures on solid media and positive intraoperative cultures, with or without an abscess or sinus tract communicating with the joint space. One hundred eight patients met our selection criteria. We excluded six patients because they had previously been treated for PJI at another institution, which left us with 102 patients for review of risk factors associated with acquiring a methicillin-resistant organism infection. The group consisted of 46 women and 56 men with a mean age at reimplantation of 67 years (range, 17–88 years). The etiology for arthritis in this cohort was osteoarthritis (93 patients), posttraumatic arthritis (four patients), rheumatoid arthritis (four patients), and hemophilia (two patients). Six patients were lost to followup, leaving us with 96 patients for review of our reinfection rate after two-stage exchange and risk factors predicting failure of this protocol. Mean time to infection from index arthroplasty was 2 years (range, 1 month to 10 years). Minimum followup was 24 months (mean, 35 months; range, 24–90 months). No patients were recalled specifically for this study: only the database and medical records were queried. Institutional review board approval was obtained before initiation of this study.

Two-stage exchange arthroplasty consisted of removal of total knee implants, as well as bone cement, irrigation and débridement of the joint, and insertion of a static antibiotic-laden cement spacer block for at least 6 weeks (mean time to reimplantation 15 weeks; range, 6–62 weeks). The cement was impregnated with 4.0 g vancomycin and 3.6 g tobramycin for each 40 g Palacos® bone cement (Biomet Inc, Warsaw, IN).

Before reimplantation, control of the infection was determined by the patient remaining afebrile with a well-healed incision, no peri-incisional erythema or drainage, and a normalization of the quantitative C-reactive protein and erythrocyte sedimentation rate.

Patients were reimplanted with cemented revision components. Simplex P® bone cement (Stryker Orthopaedics, Mahwah, NJ) with gentamicin was used at the time of the reimplantation. The type of prosthesis, whether constrained or hinged, was determined intraoperatively based on the degree of bone loss and soft tissue laxity. All surgeries were performed in operating rooms equipped with laminar flow by surgeons wearing body exhaust suits.

Methicillin-sensitive S aureus (MSSA) was the most commonly cultured organism at the time of initial resection (18%) followed by MRSA (15%), MRSE (15%), and methicillin-sensitive S epidermidis (MSSE) (13%). No organism could be isolated in 15 patients and these patients were classified as infected based on the presence of a sinus tract and/or an abscess (Table 1).

Infectious disease specialists were consulted on all cases for postoperative antibiotic management. All patients received at least 6 weeks of intravenous antibiotics. The antibiotic was chosen based on the sensitivity of the infecting organism (Table 2).

Cultures taken at the time of reimplantation were positive in 11 of 102 patients who required another round of 6 weeks of intravenous antibiotics postreimplantation. The following organisms were cultured at reimplantation: MRSE (five patients), MSSE (two patients), Proteus mirabilis (two patients), Pseudomonas aeruginosa (one patient), and MRSA (one patient). All 11 patients were infection free at time of last followup and did not require further surgery.

Detailed data including demographics, comorbidities, and surgical history were collected from the medical

Table 1. Organisms cultured preoperatively or at time of original resection

Organism	Number of patients	Percentage
MSSA	18	18
No growth	15	15
MRSA	15	15
MRSE	15	15
MSSE	13	13
Beta hemolytic Streptococcus Group B	9	9
Streptococcus Mitis	4	4
Polymicrobial	3	3
Streptococcus Pneumaniae	2	2
Escherichia Coli	2	2
Serratia Marcescens	2	2
Klebsiella Pneumoniae	1	1
Proteus Mirabilis	1	1
Pseudomonas Aeruginosa	1	1
Coryneform Striatum	1	1

Table 2. Antibiotic regimens for the different organisms

Organism	Postoperative antibiotics	Patients
Methicillin sensitive Staphlycoccus Aureus (MSSA)—18	Cefazolin	8
	Vancomycin	5
	Cefazolin/rifampin	2
	Nafcillin	2
	Linezolid/rifampin	1
No growth—15	Vancomycin	10
	Vancomycin/rifampin	2
	Vancomycin/aztreonam	1
	Vancomycin/bactrim	1
	Nafcillin	1
Methicillin resistant Staphlycoccus Aureus (MRSA)—15	Vancomycin	11
	Vancomycin/rifampin	2
	Vancomycin/zosyn	1
	Clindamycin	1
Methicillin resistant Staphlycoccus Epidermidis (MRSE)—15	Vancomycin	13
	Vancomycin/rifampin	1
	Clindamycin	1
Methicillin sensitive Staphlycoccus Epidermidis (MSSE)—13	Vancomycin	9
	Cefazolin	2
	Vancomycin/ciprofloxacin	1
	Vancomycin/rifampin	1
Beta hemolytic Streptococci Group B—9	Cefazolin	7
	Ceftriaxone	2
Streptococcus Mitis—4	Clindamycin	2
	Vancomycin	2
Streptococcus Pneumoniae—2	Ceftriaxone	2
Serratia Marcescens—2	Ciprofloxacin	2
Escherichia Coli—2	Ciprofloxacin	2
Proteus Mirabilis—1	Cefazolin	1
Coryneform Striatum—1	Ceftriaxone	1
Klebsiella Pneumoniae—1	Cefazolin/ciprofloxacin	1
Pseudomonas Aeruginosa—1	Ciprofloxacin	1
Enterococcus Faecium Group D, Serratia Marcesens—1	Vancomycin/ciprofloxacin	1
Enterococcus Faecium Group D, Escherichia Coli— 1	Vancomycin/ciprofloxacin	1
Enterococcus Faecium Group D, Pseudomonas Aeruginosa, Klebsiela Pseumoniae—1	Linezolid	1

records. Intraoperative and postoperative data were obtained from hospital records.

The means and 95% confidence intervals (CIs) were calculated for the continuous variables and were compared using the t test (parametric) and the Wilcoxon test (non-parametric) between patients in whom infection was successfully controlled and those who failed the two-stage revision procedure. Differences in categorical variables between the two groups were tested using the chi square and Fisher's exact tests. Unadjusted logistic regression analysis was performed to determine the risk factors and their odds for patients with relapsing PJI. A stepwise multivariable logistic regression analysis was implemented in our secondary analysis to determine whether any of 20 patient-related or surgically-related factors (Table 3) were associated with acquiring a methicillin-resistant organism infection before resection. All statistical analyses were performed using SAS® Version 9.1 software (SAS Institute Inc, Cary, NC).

Results

Twenty-six of the 96 patients (27%) followed at least two years experienced reinfection during followup while 70 (73%) remained free of infection. Mean time to diagnosis

Table 3. Organisms cultured during spacer revision

Organism	Number of patients
MRSA	4
No growth	4
MRSE	2
MSSA	2
Beta hemolytic Streptococcus Group B	1
Streptococcus Mitis	1
Polymicrobial	1
Escherichia Coli	1

of reinfection after component reimplantation was 468 days. Thirteen of the 26 (50%) patients who experienced reinfection were reinfected with a methicillin-resistant organism. Fourteen (54%) of these patients were reinfected with the same organism, and in 10 of the 14 (71%), the organism was methicillin-resistant. The time to reimplantation was prolonged beyond 2 months for 16 patients who underwent revision of their spacer block due to persistent infection. Six (38%) of these patients had methicillin-resistant organism infections (Table 3). Four of the 16 patients (25%) experienced reinfection requiring resection arthroplasty. One (25%) of these had a methicillin-resistant organism infection.

Patients with a PJI with a methicillin-resistant organism had a higher rate of reinfection after two-stage exchange compared to patients who did not (Table 4). The unadjusted odds of TKA infection with a methicillin-resistant organism was 3.37 (95% CI: 1.31, 8.72) times higher in patients who were subsequently reinfected compared to those who were not (Table 5).

Older age, higher body mass index, and history of thyroid disease independently predicted infection with MRSA or MRSE (Tables 6, 7).

Discussion

Two-stage exchange arthroplasty is widely accepted as the standard of care for PJI. Multiple studies have evaluated this treatment protocol and identified a variety of factors associated with failure [1–4, 6–12, 16, 17, 20, 23–26]. These include increased number of comorbidities, previous surgery, and initial diagnosis of rheumatoid arthritis versus osteoarthritis [8, 16]. Although virulence of the infecting organism has been presumed to be a risk factor for reinfection, these studies were not able to demonstrate causation between infection with a methicillin-resistant organism and failure of two-stage exchange arthroplasty.

Table 4. Characteristics of patients who failed two-stage exchange arthroplasty versus those who did not fail

Variable	Reinfection		p-Value
	Yes (n = 26)	No (n = 70)	
Age, mean (SD)	67 (10)	67 (12)	0.94
Gender, n (%)			
Male	13 (50%)	40 (57%)	0.53
Female	13 (50%)	30 (43%)	
Body mass index, mean (SD)	32 (11.50)	32 (10.71)	0.95
Smoker, n (%)			
Yes	5 (19%)	6 (9%)	0.15
No	21 (81%)	64 (91%)	
Type of infection, n (%)			
Acute	15 (58%)	23 (33%)	0.39
Chronic	11 (42%)	47 (67%)	
Prior I&D, n (%)			
Yes	9 (35%)	22 (31%)	0.77
No	17 (65%)	48 (69%)	
Methicillin resistant, n (%)			
Yes	13 (50%)	16 (23%)	0.01
No	13 (50%)	54 (77%)	
Thyroid, n (%)			
Yes	1 (4%)	11 (16%)	0.12
No	25 (96%)	59 (84%)	
Diabetes, n (%)			
Yes	5 (19%)	18 (26%)	0.51
No	21 (81%)	52 (74%)	
Inflammatory arthropathy, n (%)			
Yes	3 (12%)	6 (9%)	0.66
No	23 (88%)	64 (91%)	
Steroid use, n (%)			
Yes	2 (8%)	2 (3%)	0.29
No	24 (92%)	68 (97%)	
Prophylactic antibiotics, n (%)			
Yes	7 (27%)	14 (20%)	0.47
No	19 (71%)	56 (80%)	
ASA score, mean (SD)	2.73 (0.45)	2.73 (0.61)	0.87
EBL (mL), mean (SD)	90 (109)	90 (77)	0.95
Tourniquet time, mean (SD)	110 (24)	105 (25)	0.27
Wound class, n (%)			
1	9 (35%)	25 (36%)	0.92
2/3/4	17 (65%)	45 (64%)	
Complications of resection, n (%)			
Yes	3 (12%)	14 (20%)	0.34
No	23 (88%)	56 (80%)	
Resection performed again, n (%)			
Yes	5 (19%)	8 (11%)	0.32
No	21 (81%)	62 (89%)	

Table 4. continued

Variable	Reinfection		p-Value
	Yes (n = 26)	No (n = 70)	
Prosthesis type, n (%)			
Constrained	3 (12%)	13 (19%)	0.41
Hinged	23 (88%)	57 (81%)	
Complications after reimplantation, n (%)			
Yes	4 (15%)	5 (7%)	0.22
No	22 (85%)	65 (93%)	

I&D = irrigation and débridement; ASA = American Association of Anesthesiology; EBL = estimated blood loss.

Table 5. Logistic regression analysis comparing patients who failed two-stage exchange arthroplasty versus those who did not fail

Variables	Odds ratio	95% CI	p-Value
Methicillin resistance	3.37	1.31; 8.72	0.01

We therefore asked the following questions: (1) What is our reinfection rate after two-stage exchange arthroplasty? (2) Which risk factors predict failure of the two-stage exchange arthroplasty procedure? And (3) which variables may have predisposed our patient population to infection with a methicillin-resistant organism?

Like all epidemiologic studies, there are important limitations to consider. First, the nonrandomized study design precludes the ability to control for unknown or unmeasured confounders. Second, although all patients were treated surgically with removal of implants, thorough irrigation and débridement, and placement of an antibiotic-impregnated spacer, the variability of the specifics of the procedure among surgeons may introduce misclassification bias (failure to adequately perform any step of the procedure; the débridement, for example, could lead to recurrent infection that may have been otherwise avoided). Therefore, a patient may have been misclassified as a failure due to the virulence of the organism when in fact, it may have been due to the manner in which the procedure was performed. Similarly, we did not have a set protocol for postoperative antibiotic treatment resulting in some patients receiving a single-agent regimen while others received a multiagent regimen. Finally, although our sample size is relatively large, some important factors may not have been identified due to the study being underpowered. However, we believe our findings provide valuable information to patients in making informed decisions about their healthcare, help physicians in appropriate patient selection and through further research create opportunities to develop tailored protocols for these patients.

Table 6. Baseline patient and index procedure characteristics of subjects who had an infection with a methicillin resistant organism versus those who had an infection with a nonmethicillin resistant organism

Variables	Methicillin resistant		p-Value
	Yes (N = 30)	No (N = 72)	
Age, mean (SD)	69.77 (9.15)	66.08 (12.32)	0.10
Sex, n (%)			
Male	15 (50%)	41 (56.94%)	0.52
Female	15 (50%)	31 (43.06%)	
BMI, mean (SD)	35.58 (13.56)	30.07 (8.77)	0.05
Smoker, n (%)			
Yes	2 (6.67%)	10 (13.89%)	0.31
No	28 (93.33%)	62 (86.11%)	
Type of infection, n (%)			
Acute	10 (33.33%)	24 (33.33%)	1.0
Chronic	20 (66.67%)	48 (66.67%)	
Prior I&D, n (%)			
Yes	8 (26.67%)	25 (34.72%)	0.43
No	22 (73.33%)	47 (65.28%)	
Primary versus revision, n (%)			
Primary	20 (66.67%)	57 (79.17%)	0.18
Revision	10 (33.33%)	15 (20.83%)	
Thyroid disease, n (%)			
Yes	6 (20%)	6 (8.33%)	0.09
No	24 (80%)	66 (91.67%)	
Diabetes mellitus, n (%)			
Yes	7 (23.33%)	17 (23.61%)	0.98
No	23 (76.67%)	55 (76.39%)	
Inflammatory arthropathy, n (%)			
Yes	4 (13.33%)	6 (8.33%)	0.44
No	26 (86.67%)	66 (91.67%)	
COPD and asthma, n (%)			
Yes	5 (16.67%)	13 (18.06%)	0.87
No	25 (83.33%)	59 (81.94%)	
Steroid use, n (%)			
Yes	3 (10%)	2 (2.78%)	0.12
No	27 (90%)	70 (97.22%)	
UTI, n (%)			
Yes	2 (6.67%)	6 (8.33%)	0.78
No	28 (93.33%)	66 (91.67%)	
High cholesterol, n (%)			
Yes	4 (13.33%)	17 (23.61%)	0.24
No	26 (86.67%)	55 (76.39%)	
Malignancy, n (%)			
Yes	4 (13.33%)	19 (26.39%)	0.15
No	26 (86.67%)	53 (73.61%)	
Chronic renal failure, n (%)			
Yes	2 (6.67%)	4 (5.56%)	0.82
No	28 (93.33%)	68 (94.44%)	

Table 6. continued

Variables	Methicillin resistant		p-Value
	Yes (N = 30)	No (N = 72)	
Depression, n (%)			
Yes	4 (13.33%)	5 (6.94%)	0.30
No	26 (86.67%)	67 (93.06%)	

BMI = body mass index; I&D = irrigation and débridement; COPD = chronic obstructive pulmonary disease; UTI = urinary tract infection.

Table 7. Stepwise logistic regression analysis including variables which were significant ($p < 0.10$) in univariate analysis of infections with methicillin resistant organisms versus nonmethicillin resistant organisms

Variables	Odds ratio	95% CI	p-Value
Age	1.09	1.02; 1.16	0.009
BMI	1.10	1.03; 1.16	0.002
Thyroid	5.44	1.19; 24.82	0.03

BMI = body mass index.

Our reinfection rate (27%) after two-stage exchange arthroplasty is on the high end of what is reported in the literature (Table 8) [5, 6, 8, 16]. This may be explained by our study representing a worst-case scenario: although only 19 of the 26 patients who were classified as reinfected underwent subsequent resection arthroplasty, any additional surgery after the initial reimplantation, even if the prosthesis was retained, was considered a failure. Previous reports in the literature [16, 23] do not consider infection with a different organism or reoperation as a failure if the prosthesis is retained. We believe the need for further surgery and administration of prolonged therapeutic or suppressive antibiotics should be considered a failure. Our time to reinfection (66 weeks), reinfection with a methicillin-resistant organism (50%), and reinfection with the same organism as the index infection (56%) are consistent with data from other studies [5, 6, 8, 16]. These findings suggest our higher reinfection rate is unlikely the result of intraoperative or early postoperative management of the patients as we did not see a rise in acute infections and were similarly competent at controlling the index organism. Our analysis of patients undergoing revision of their spacer for persistent infection suggests that this protocol may be used with similar outcomes as a standard two-stage exchange arthroplasty.

In our assessment of predictors of failure after two-stage exchange arthroplasty, our study shows a correlation with methicillin-resistant organism infections. Previous studies [6, 8, 11, 12, 16] have demonstrated lower satisfaction ratings among patients, increased number of surgical procedures (3.9 per patient) and lower rates of controlling infections (18–76%) in the setting of methicillin-resistant organism infections after primary TKA. The largest published study [6], 96 knees in 94 patients, did not find methicillin-resistant organism infections to be associated with failure of two-stage exchange but suggested this likely represented a Type II statistical error. Our findings serve to confirm what has long been presumed by the orthopaedic community, highlight the need for close followup of these patients for signs of recurrent infection, and expose the possibility that our current treatment strategies may be inadequate when dealing with more virulent organisms.

Although the authors are not aware of a study reporting the risk factors of acquiring a methicillin-resistant PJI, multiple studies [13, 15, 19, 21, 22] have addressed predictors for PJI with any organism. Kurtz et al. [13] evaluated the Medicare population and demonstrated a higher rate of infection in men, patients with comorbidities represented by a nonzero Charlson index score, longer-duration procedures, and patients receiving public assistance. Pulido et al. [19] identified a higher American Society of Anesthesiologists score, morbid obesity, bilateral arthroplasty, allogenic transfusion, postoperative atrial fibrillation, myocardial infarction, urinary tract infection, and longer hospitalizations to be associated with PJI. In reviewing the infectious disease literature, there are substantial data describing the risk factors associated with acquiring a soft tissue methicillin-resistant infection. These factors include a prior history of a MRSA infection,

Table 8. Comparative literature

Author	n (Knees)	Reinfection after two-stage exchange arthroplasty	Time to reinfection (weeks)	Reinfection with a methicillin-resistant organism	Reinfection with same organism as index infection
Mittal et al. [16]	37	9/37 (24.32%)		9/9 (100.00%)	4/9 (44.44%)
Hirakawa et al. [8]	55	14/55 (25.45%)	50.8	2/14 (14.29%)	10/14 (71.43%)
Haleem et al. [6]	96	9/96 (9.38%)	52.0		4/9 (44.44%)
Goldman et al. [5]	64	6/64 (9.38%)	98.8		2/6 (33.33%)
Kurd et al. [current study]	96	26/96 (27.08%)	66.9	13/26 (50.00%)	14/26 (53.85%)

residing in a long-term care facility or hospital admission in the preceding 12 months, intravenous drug use, recent antibiotic use, diabetes mellitus, HIV, and abscess formation [15, 21, 22]. Our data suggest a higher risk of PJI with a virulent organism among older patients, patients with a higher body mass index, and patients with a history of thyroid disease. These findings suggest an association between a weakened or ill-functioning immune system and methicillin-resistant PJI. However, we found no such association among other factors affecting the immune system: history of steroid use, diabetes, and inflammatory arthropathy. The inconsistency of these results makes it difficult to explain why these patients are more likely to acquire methicillin-resistant PJI.

PJI after TKA continues to be a devastating complication that is commonly treated with a two-stage exchange arthroplasty. While this protocol has demonstrated good results when treating more indolent infections, its application to resistant organism infections cannot be assumed. Our data demonstrate increasing reinfection rates and a higher failure rate among patients with resistant organism infections. This presents a growing problem for the orthopaedic community as current treatment protocols may not be adequate to control these virulent pathogens.

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