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Revision Total Knee Arthroplasty Infection

Incidence and Predictors

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Abstract

Background Deep infection remains one of the most devastating and costly complications after total knee arthroplasty (TKA). The risk of deep infection after revision TKA is reportedly greater than that for primary TKA; however, we do not know the exact incidence of infection after revision TKA.

Questions/purposes We determined the incidence of infection after revision, the type of microorganisms involved and TKA, and the potential risk factors for this infection.

Methods We retrospectively reviewed 475 patients (476 knees) with 499 TKA revisions performed between March 1998 and December 2005. Of the 476 knees, 91 (19%) were revised for infection and 385 (81%) were revised for aseptic failure. Preoperative history, results of physical examinations, laboratory and radiographic results, joint fluid aspiration results along with analysis of intraoperative findings were all considered to make an assessment of septic versus aseptic failure modes. Patients were followed for a minimum of 25 months (mean, 65 months; range, 25–159 months).

Results Deep infection developed in 44 of the 476 knees (9%). The infection rate was higher in patients undergoing revision for infection than in patients with aseptic revisions: 21% (23 of 91) and 5% (21 of 385), respectively. Revision for infection, higher Charlson index, and diagnosis other than osteoarthritis at the time of primary TKA predicted infection of the revision. The risk of infection for patients undergoing TKA revisions was 10-fold higher than for patients undergoing primary TKA at our institution.

Conclusions Infection of primary TKA is the most important risk factor for subsequent infection of TKA revisions.

Level of Evidence Level III, 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 approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Infection is one of the most dreaded complications after TKA. Treatment of infection may be associated with numerous challenges, including the need for multiple operations, longer hospitalization, higher incidence of morbidity and mortality, and increased cost [18, 23, 32, 33]. Although implementation of various strategies such as the administration of prophylactic antibiotics has reduced the incidence of infection after primary arthroplasty to approximately 1% to 2% [20], orthopaedic surgeons encounter this complication on a frequent basis [19, 20, 26, 36]. Infection after revision surgery occurs even more frequently and poses a complex problem [16, 33, 40]. Periprosthetic joint infection is reportedly the most

common mechanism of implant failure after revision TKA, accounting for 46% of failures in one study [38].

The risk factors for periprosthetic joint infection after primary knee arthroplasty include male gender, rheumatoid arthritis, previous fracture around the knee, and wound-related complications [1, 2, 8, 15, 16, 21, 23, 28, 40]. However, risk factors after revision arthroplasty are unclear and it is not known if those for patients undergoing primary TKA also apply to those having revision arthroplasty. The incidence varies from 0% to 10% [10, 11, 13, 14, 25, 29, 34, 35, 37]. The reason for these variations relates to multiple factors, including the definition of infection, the type of cohort included, sample size, and the duration of followup. In light of the high economic impact and increasing number of infected revisions, better knowledge of modifiable factors that make TKA revisions vulnerable to infection might help guide clinical practice in the treatment and prevention of this complication.

We determined (1) the incidence of infection in a relatively large cohort undergoing revision TKA; (2) the microorganisms causing these infections; and (3) whether comorbidities, age, gender, the length of time between primary and revision TKA, blood transfusions, operative time, the reason for revision surgery, and the type of treatment modalities in revisions for infection predicted subsequent periprosthetic joint infection (PJI) after revision TKA.

Patients and Methods

We retrospectively reviewed prospectively collected data on all 499 revision TKAs performed in 475 patients at our institution between March 1998 and December 2005. We limited our analysis to patients in whom the index revision was the first revision after primary TKA, so we excluded 13 patients (13 knees) with previous revision and nine patients (10 knees) that had the first stage of a two-stage revision performed at another institution, leaving 451 patients (476 knees). Of these, 385 revisions were for infection and 91 were for aseptic causes of failure. The index revision surgery was defined as any procedure in which at least tibial, patellar, femoral, or polyethylene components were exchanged. All patients who underwent revision surgery received prophylactic antibiotics until intraoperative cultures were cleared negative (usually at 48 hours). We attempted to optimize the patients' medical conditions, such as blood glucose levels, prior to the surgery and patients were asked to halt or reduce smoking. Multistage revisions from removal of the old implant to insertion of a new implant were treated as a single procedure. Periprosthetic joint infection was diagnosed based on the presence of one or more of the following criteria: (1) abscess or sinus tract that communicated to the joint space; (2) positive growth on solid medium from joint aspiration fluid or intraoperative culture; (3) purulence detected intraoperatively; or (4) an elevated cell count and differential of the aspirate fluid and abnormal erythrocyte sedimentation rate (0.30 mm/hr) or C-reactive protein greater than 10 mg/dL. The reasons for revision were determined by the attending orthopaedic surgeon based on preoperative history, physical examination, laboratory and radiographic findings, and joint fluid aspiration results, if applicable, along with the analysis of intraoperative findings, including examination under anesthesia and gross inspection of the components, tissue, and fluid. Patients were followed for a minimum of 25 months (mean, 65 months; range, 25–159 months). No patients were lost to followup. Patients with no recent followup were contacted by telephone or asked to return for followup.

Periprosthetic infection in the cohort of 91 patients undergoing revision arthroplasty for infection was treated according to the institutional protocols. The majority (88%) of patients were treated with two-stage exchange arthroplasty. Eight patients (9%) were treated with irrigation and débridement along with exchange of the tibial polyethylene insert. Three patients (3%) underwent one-stage exchange arthroplasty that included removal of prosthetic components, débridement of the cement and infected tissues, and insertion of new prosthetic components using antibiotic-impregnated cement under the same anesthesia.

We recorded patient- and surgery-related factors as potential predictors of infection after revision TKA: age at the time of index revision, side of surgery, gender, diagnosis at the time of primary TKA, the length of time between primary and revision TKA, the reason for revision TKA, body mass index at the time of revision, American Society of Anesthesiology score [9] and Charlson index [7], operative time, and comorbidities at the time of index revision. We tried to consider all potential risk factors based on previous studies on infection following primary TKA. The indications for revision were categorized as infection, arthrofibrosis, aseptic loosening, extensor mechanism problems, instability, fracture, malpositioning/malalignment, and wear. When applicable, multiple reasons for revision were noted, but each patient was categorized, for the purpose of the analysis, into a septic or aseptic failure group. In addition, aseptic loosening of the components was always treated as a secondary reason when found in conjunction with another etiology that accounted for failure.

Preliminary univariate data analysis to determine potential predictors included nonparametric and parametric two-tailed tests; categorical data were evaluated using two-sided Fisher's exact tests, and continuous variable were compared by Student's t test ($p < 0.05$). Then we included all factors significant in the unadjusted analysis and

performed a step-wise multiple logistic regression analysis to control for confounding variables and determine the effects of different patient- or procedure-related factors on the risk of infection after index revision TKA. Hazard ratios along with 95% confidence intervals calculated with adjusted models were reported for septic revisions. All statistical analyses were conducted using STATA 10.0 (College Station, TX).

Results

Deep infection after revision TKA developed in 44 patients (44 knees). Nineteen of these infections (43%) occurred within the first 3 months following surgery, whereas the remaining 25 (57%) occurred as late infections (after 3 months). The average time from index revision to reoperation for infection was 13.2 months (range, 0.1–71 months). The overall incidence of infection after revision TKA was 9.2% (44 of 477). The incidence of infection was fourfold higher at 20.7% after revisions that were performed for septic failure (23 of 91) compared with an infection rate of 5.4% (21 of 385) after revision for aseptic failure.

The most prevalent organism isolated from infected revision surgeries was Staphylococcus aureus (27%) followed by Staphylococcus epidermidis (16%), Streptococcus group B (4.6%), Proteus mirabilis (4.6%), Streptococcus mitis (2.2%), Pseudomonas aeruginosa (2.2%), Citrobacter spp. (2.2%), Enterobacter faecalis (2.2%), and Candida albicans (2.2%). Of 19 staphylococcal organisms, five were methicillin-resistant S. aureus and six were methicillin-resistant S. epidermidis (57% methicillin-resistant). In 16 (36%) patients with infected TKA revisions, no organism could be isolated despite the fact there was other evidence for periprosthetic infection leading to failure.

The failure rate for treatment of periprosthetic infection was higher ($p = 0.02$) in patients undergoing irrigation and débridement or one-stage exchange arthroplasty compared with that for patients undergoing two-stage exchange arthroplasty; 54% (six of 11) had a 21% failure rate (17 of 80). The failure rate was also higher ($p = 0.03$) in the group of patients with methicillin-resistant infections (47% versus 20%). In the unadjusted univariate analysis, we identified the following patient (Table 1) and surgical (Table 2) factors predicting a higher risk of failure: medical comorbidities (in particular connective tissue disorder and respiratory disease), diagnosis other than osteoarthritis at the time of primary TKA, revision for infection, abnormal serology at the time of revision arthroplasty, and one-stage surgical treatment for infection (irrigation and débridement or one-stage exchange arthroplasty). The independent predictors of infection after revision TKA in the multivariate model were diagnosis other than osteoarthritis at the time of primary TKA, higher Charlson index, and revision for infection. Using time to event analysis in which subjects were followed until reoperation because of infection or censorship (as a result of loss to followup), patients with septic indication for revision had a higher risk of developing infection than subjects who had an aseptic indication for revision. The hazard ratio was 2.14 (95% confidence interval, 1.41–3.25; $p < 0.01$) in unadjusted analysis and 2.24 (95% confidence interval, 1.31–3.82; $p < 0.01$) when adjusting for all potential confounders (including age, gender, comorbidities, transfusion, and positive serology).

Discussion

It has generally been believed that the infection rate after revision TKA is substantially higher than the infection rate after primary TKA [12, 27, 41]. However, the rate of infection after revision TKA varies greatly between 0% and 10% according to different studies [10, 11, 13, 14, 25, 29, 34, 35, 37]. The majority, if not all, of previous studies evaluate the incidence of infection after revision for aseptic failure. We conceived this study to examine the rate of periprosthetic infection after revision TKA, to identify the current microorganisms involved in infections after revision, and to determine risk factors for infection after revision TKA.

We acknowledge some limitations of our study. First, because of the retrospective design, the study is likely to have been affected by confounding variables that could not be controlled, including variability in data collection, potential bias, and missing data for some patients. Despite all efforts, some data could not be collected. However, we did not believe the missing data were critical to influence the conclusions of this study. The prospective and strict data collection process that was in place, however, should have reduced the influence of some the aforementioned variables in the analysis. Second, because of the relatively low incidence of infections after revision TKA, our analysis may have failed to detect some important risk factors. However, the study is based on a relatively large cohort of patients who underwent revision arthroplasty in one institution over a relatively short period of time and who were subjected to the same care protocols. Third, because it was not our intention to report all-time incidence of infection, but merely to follow patients for at least 2 years after revision, the true incidence of infection in this cohort is likely underestimated. Fourth, the limitation of current diagnostic methods to identify infection or isolate the infecting organism may result in erroneously categorizing these patients into aseptic failures. Finally, we didn't

Table 1. Univariate analysis of different potential preoperative risk factors for infection after revision TKA

Patients' factors	Infection (n = 44)	No infection (n = 432)	Univariate odds ratio (95% confidence interval)	p Value
Age (mean, SD), years	65.95 (11.61)	66.67 (10.96)	0.99 (0.97–1.02)	0.68
Male gender (number, %)	22 (50.00%)	155 (35.88%)	1.79 (0.96–3.33)	0.07
Body mass index 25 kg/m^2 or greater (number, %)	31.53 (9.54)	33.18 (8.14)	0.97 (0.93–1.02)	0.22
ASA score (mean, SD)	2.45 (0.82)	2.36 (0.77)	1.17 (0.77–1.77)	0.46
Charlson index (mean, SD)	4.07 (3.00)	2.81 (1.60)	1.35 (1.16–1.56)	< 0.01
Charlson index greater than 3 (number, %)	22 (50.00%)	124 (28.70%)	2.48 (1.33–4.65)	< 0.01
Diagnosis other than osteoarthritis (number, %)	7 (15.91%)	20 (4.63%)	3.90 (1.55–9.82)	< 0.01
Inflammatory arthritis (number, %)	8 (18.18%)	32 (7.41%)	2.78 (1.19–6.48)	0.02
Comorbidities				
Hypertension (number, %)	26 (59.09%)	231 (53.47%)	1.26 (0.67–2.36)	0.48
Diabetes mellitus (number, %)	14 (31.82%)	99 (22.92%)	1.57 (0.81–3.08)	0.19
Cardiac (number, %)	15 (34.09%)	118 (27.31%)	1.38 (0.71–2.66)	0.34
Respiratory (number, %)	15 (34.09%)	70 (16.20%)	2.67 (1.36–5.25)	< 0.01
Gasterointestinal (number, %)	14 (31.82%)	105 (24.31%)	1.45 (0.74–2.84)	0.28
Cerebrovascular (number, %)	1 (2.27%)	8 (1.85%)	1.23 (0.15–10.09)	0.85
Renal (number, %)	2 (4.55%)	7 (1.62%)	2.89 (0.58–14.36)	0.19
Liver (number, %)	4 (9.09%)	16 (3.70%)	2.60 (0.83–8.15)	0.10
Thyroid (number, %)	5 (11.36%)	53 (12.27%)	0.92 (0.35–2.43)	0.86
Vascular arterial (number, %)	4 (9.09%)	29 (6.71%)	0.51 (0.18–1.47)	0.21
Vascular venous (number, %)	4 (9.09%)	29 (6.71%)	1.39 (0.47–4.15)	0.56
Cancer (number, %)	8 (18.18%)	50 (11.57%)	1.70 (0.7–3.86)	0.21

ASA = American Society of Anesthesiology.

Table 2. Univariate analysis of different potential operative risk factors for infection after revision TKA

Surgical factors	Infection (n = 44)	No infection (n = 432)	Univariate odds ratio (95% confidence interval)	p Value
Bilateral (number, %)	7 (15.91%)	43 (9.95%)	1.71 (0.72–4.07)	0.22
Duration primary to secondary (mean, SD)	3.64 (3.70)	4.79 (4.57)	0.94 (0.86–1.02)	0.12
Indication (number, %)				
Arthrofibrosis	1 (2.27%)	48 (11.11%)	0.19 (0.03–1.38)	0.10
Extensor	2 (4.55%)	48 (11.11%)	0.38 (0.09–1.62)	0.19
Fracture	0	21 (4.86%)	—	—
Instability	0	40 (9.26%)	—	—
Mechanical	2 (4.55%)	11 (2.55%)	1.82 (0.39–8.50)	0.45
Wear	3 (6.82%)	61 (14.12%)	0.45 (0.13–1.48)	0.19
Sepsis	23 (52.27%)	68 (15.74%)	5.86 (3.07–11.18)	< 0.01
Loosening	13 (29.55%)	135 (31.25%)	0.96 (0.51–1.79)	0.90
Operative time (mean, SD), minutes	139.08 (45.78)	148.13 (46.46)	0.99 (0.99–1.00)	0.24
Unit transfused (mean, SD)	0.86 (0.89)	1.12 (1.11)	0.78 (0.50–1.23)	0.29
Transfusion (number, %)	13 (29.55%)	280 (64.81%)	0.23 (0.12–0.45)	< 0.01
ESR (mean, SD), mm/hr	49.21 (37.25)	34.05 (24.31)	1.02 (1.01–1.03)	< 0.01
ESR 30 or greater (number, %)	23 (60.53%)	180 (47.49%)	1.70 (0.86–3.35)	0.13
CRP (mean, SD)	9.96 (13.29)	2.62 (7.61)	1.06 (1.03–1.10)	< 0.01
CRP 10 or greater (number, %)	21 (60.00%)	128 (40.76%)	2.18 (1.07–4.45)	0.03

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Table 3. Reported spectrum of microorganisms in primary and revision TKA

Author	Cohort	Microorganisms
Segawa et al. [33] 1999	TKA*	Staphylococcus 71% Streptococcus 21% Gram negative 4% No organism growth 2%
Peersman et al. [23] 2001	Primary and revision TKA	Staphylococcus 54% Streptococcus group B 6% Gram negative 4% Polymicrobial 9% Other 11% No organism growth 19%
Blom et al. [4] 2004	Primary and revision TKA	Primary Staphylococcus 66% Polymicrobial 23% No organism growth 11% Revision Staphylococcus 100%
Pulido et al. [28] 2008	Primary TKA	Staphylococcus 50% Streptococcus 14.5% Gram negative 14.5% Polymicrobial 6% Coryneform striatum 2% No organism growth 13%
Mortazavi et al. [current study]	Revision TKA	Staphylococcus 43% Streptococcus group B 4.6% Gram negative 11.2% Candida albicans 2.2% No organism growth 36%

*TKA = Total Knee Arthroplasty.

evaluate postoperative risk factors for infection. The adverse influence of perioperative complications such as hematoma and wound problem on the subsequent infection is well-known.

Our data demonstrate the rate of infection after revision arthroplasty at 9.2% is considerably higher than the rate of infection after primary TKA at 0.5% to 1% at our institute [28]. It also demonstrates the rate of infection after revision for septic reasons is over fourfold higher than the rate of infection after revision TKA for aseptic reasons. The latter is not difficult to understand because numerous studies have identified history of infection as an important predictor for periprosthetic infection [2, 30]. However, the rate of infection after revision for aseptic reason is still fivefold higher than the rate of infection after primary TKA. It is plausible periprosthetic infection was indeed the cause of failure of TKA in these patients but escaped detection using conventional methods for diagnosis.

We found the Gram-positive organisms S. aureus and S. epidermidis were the most frequently isolated microorganisms from infected revision TKA. The distribution of pathogens was comparable to those causing primary TKA infections [4, 23, 28, 33] (Table 3). In approximately one-fourth of patients who had clinically diagnosed infection, no pathogens could be cultured in infected primary or revision knees. The most important reported reason for negative cultures is the inappropriate administration of antibiotics before aspiration [23].

Our study also revealed some factors known to predispose patients to infection. Although all the previous studies identifying these risk factors for infection were conducted in cohorts of patients undergoing primary TKA, it is not surprising to observe these factors as being important predictors of infection after revision TKA also [23, 27, 28, 30, 40] (Table 4). Diagnosis other than osteoarthritis and medical comorbidities were among those factors. Other important risk factors for infection such as diabetes and obesity were not independent risk factors in the logistic regression analysis. The latter may relate to the relatively small sample size of patients with events (infection) (ie, Type II error). While operative time or blood transfusion [24, 30] did not predict failure, our findings may relate to the complexity of revision surgery, the relatively long operative times, and the large number of patients who received transfusions; thus, we could not definitely determine the relative importance of these factors. We did not differentiate between early and late infection following revision in the analysis for risk factors for several reasons. First, we think that the presence of risk factors predisposes the patients to infection even as a late event. Additionally, there is no clear cut-off point to categorize acute and chronic infections. Finally, it is possible that some of these patients with late infection may have had contamination during surgery leading to infection that declared itself at a later date. The failure rate of surgical treatment of infected TKA was considerably higher when one-stage exchange arthroplasty or irrigation and débridement together with exchange of polyethylene was attempted. The failure was also higher if the infecting organism exhibited methicillin resistance. Taken together, these issues raise the question as to whether irrigation and débridement or one-stage exchange arthroplasty should be attempted in patients with periprosthetic infection, particularly those caused by resistant organisms. In an analysis conducted by the Periprosthetic Infection Study Group that collates data from multiple centers, failure of irrigation and débridement was higher than 70% for infections caused by methicillin-resistant organisms [6, 17, 31]. Based on these findings, we do not currently advocate irrigation and débridement or one-stage exchange arthroplasty for periprosthetic infection caused by methicillin-resistant organisms, even for early

Table 4. Reported risk factors for infection after total joint arthroplasty

Author	Study type		Procedure	Risk factors
Berbari et al. [2] 1998	Case-control	PJI	Primary hip and knee arthroplasty	Surgical site infection not involving the prosthesis, NNIS surgical patient risk score of 1 or 2 Presence of malignancy History of joint arthroplasty
Dowsey et al. [8] 1999	Case-control	PJI	Primary TKA	Morbid obesity Combined obesity and diabetes Male gender
Peersman et al. [23] 2001	Case-control	PJI	Primary and revision TKA	Higher body Weight Increasing number of other comorbidities Diagnosis other than osteoarthritis Revision surgery
Saleh et al. [30] 2002	Case-control	Deep Wound infection	TKA and THA	Hematoma formation Persistent postoperative drainage
Peersman et al. [24] 2006	Case-control	PJI	TKA	Operative time
Babkin et al. [1] 2007	Case-control	Superficial and deep infection	TKA	Left knee Prosthesis type
Pulido et al. [28] 2008	Case-control		Primary TKA or THA	High ASA score Morbid obesity Bilateral arthroplasty Knee arthroplasty Allogenic transfusion Postoperative atrial fibrillation Myocardial infarction Urinary tract infection Longer hospitalization
Bongartz et al. [5] 2008	Case-control	PJI	Primary and revision TKA and THA	Rheumatoid Arthritis For RA patients Revision Previous PJI
Jamsen et al. [15] 2009	Register-based study	PJI	Primary and revision TKA	Primary Male gender RA Previous fracture Constrained or hinge prosthesis Wound related Complications Revision Revision Revision for the treatment of infection Wound healing problems
Mortazavi et al. [current study]	Case-control study	PJI	Revision TKA	diagnosis other than osteoarthritis at the time of primary TKA higher Charlson index revision for infection

infections. Even with two-stage exchange arthroplasty, reinfection or recurrence of infection still occurs in 9% to 14% of patients [22]. The failure rate of two-stage exchange arthroplasty in our series was somewhat higher at 21%. Of the 80 patients who had a previous infection and underwent revision TKA, 17 experienced a subsequent

prosthetic joint infection. One major reason for the higher failure rate in our series may relate to definition of failure, which was described as need for any further surgical intervention or antibiotic treatment. The incidence of initial infection with methicillin-resistant organisms was also much higher in our series, which may have contributed to the higher failure rates observed by other investigators [17, 31]. Our institutional protocols use multiple methods, including serologic tests and aspiration of the joint for cell count, neutrophil percentage, and culture, before reimplantation. Despite these strict protocols, some of the reinfections were caused by the same initial infecting organism pointing to the possibility that persistence of infection was responsible for failure in some of these patients. The latter again highlights the limitations of current diagnostic modality for PJI that fails to detect an organism in some cases. With improvements in diagnosis of periprosthetic infection such as sonication [39] or the use of molecular techniques [3], we believe more of these patients with "aseptic" failures will be correctly diagnosed as infected and treated appropriately. In a study by Bongartz et al., the rate of periprosthetic infection was 3.5% in patients with a history of infection in other prosthetic joints [5]. The rate of infection increased to 29.9% in a joint that had previously been treated for periprosthetic infection. The authors concluded reinfections are the result of undetected persistence of bacteria and not the result of general host susceptibility to infections [5]. One drawback of the latter study, however, is it did not consider revision surgery as a potential confounding factor for increased risk of infection.

It appears that the risk of infection after revision TKA is considerably higher than infection after primary TKA. Treating periprosthetic infection following revision TKA remains challenging. All efforts should be made to minimize this complication. Thorough preoperative evaluation of all patients undergoing revision TKA is an important strategy if unexpected infections following revision TKA are to be minimized.

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