

# Bacteriology and risk factors associated with periprosthetic joint infection after primary total knee arthroplasty: retrospective study of 2543 cases

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## ABSTRACT

**Introduction:** Periprosthetic joint infection after total knee arthroplasty is a serious complication. This study aimed to identify risk factors and bacteriological features associated with periprosthetic joint infection after primary total knee arthroplasty performed at a teaching hospital.

**Methods:** We reviewed 2543 elective primary total knee arthroplasties performed at our institution from 1993 to 2013. Data were collected from the Hong Kong Hospital Authority's Clinical Data Analysis and Reporting System, the Infection Control Team, and the joint replacement division registry. The association between potential risk factors and periprosthetic joint infection was examined by univariable analysis and multivariable logistic regression. Univariable analyses were also performed to examine the association between potential risk factors and bacteriology and between potential risk factors, including bacteriology, and early-onset infection.

**Results:** The incidence of periprosthetic joint infection in our series was 1.34% (n=34). The incidence of early-onset infection was 0.39% (n=24). Of the periprosthetic joint infections, 29.4% were early-onset infections. In both univariable and multivariable analyses, only rheumatoid arthritis was a significant predictor of periprosthetic joint infection. Methicillin-sensitive *Staphylococcus*

*aureus* was the most common causative organism. We did not identify any significant association between potential risk factors and bacteriology. Periprosthetic joint infection caused by skin flora was positively associated with early-onset infection but the association was not statistically significant.

**Conclusion:** The incidence of periprosthetic joint infection after elective primary total knee arthroplasty performed at our institution from 1993 to 2013 was 1.34%. Rheumatoid arthritis was a significant risk factor for periprosthetic joint infection.

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### New knowledge added by this study

- The incidence of periprosthetic joint infection after elective primary total knee arthroplasty performed at our institution from 1993 to 2013 was 1.34%.
- Rheumatoid arthritis was the only significant risk factor identified in the series.

### Implications for clinical practice or policy

- Early-onset infection may be associated with infection with skin flora. Therefore, in early-onset periprosthetic joint infection with negative cultures, an empirical antibiotic regimen should preferably provide adequate coverage against skin flora organisms.

## Introduction

Periprosthetic joint infection (PJI) is an uncommon but serious complication after total knee arthroplasty (TKA). Treatment is often challenging and has a major impact on the patient. Multiple operations are often required and patients suffer from

a long period of disability. Moreover, PJI incurs considerable health care costs.<sup>1-3</sup> Therefore, multiple strategies including antibiotic prophylaxis, body exhaust systems, and laminar airflow systems have been developed to reduce the incidence of PJI. Studies have also identified modifiable risk factors

for PJI after elective total joint replacement,<sup>4-14</sup> with the aim of further reducing the incidence of PJI. However, local data on the risk factors and bacteriological features associated with PJI are still lacking.

This study had several aims. First, it aimed to provide the most up-to-date local data on incidence of and risk factors for PJI, including age, sex, presence of diabetes, presence of rheumatoid arthritis, and one-stage bilateral TKA. Second, this study aimed to provide an update on the bacteriology of PJI after elective primary TKA and to examine the association between potential risk factors and bacteriology. Third, we attempted to determine which risk factors, including bacteriology, were more likely to be associated with early-onset infection after elective primary TKA.

It is hoped that risk factors can be optimised or modified to prevent infection after TKA. Furthermore, an improved understanding of local bacteriological patterns and their relationship with various risk factors can help guide antimicrobial therapy.

## Methods

We reviewed 2543 elective primary TKAs performed at the Queen Mary Hospital, Hong Kong, from 1993 to 2013. Data were collected by an infection control nurse of the Department of Microbiology who was blinded to the study objectives. The cohort data were collected from the Hong Kong Hospital Authority's Clinical Data Analysis and Reporting System, the Infection Control Team, and the hospital's joint replacement division registry. The keywords used in the data search were 'periprosthetic joint infection', 'total knee arthroplasty', and 'surgical site infection'. Revision arthroplasties and knee arthroplasties for malignant conditions were excluded from the study. In patients with a history of native joint infection, elective primary TKA was performed only after eradication of the infection. Patients with active bacteraemia were also precluded from elective primary TKA until they were infection-free. There were no cases of severe immunosuppression. In relation to infection control, the majority of perioperative protocols for primary TKA were the same throughout the study period. Preoperatively, intravenous antibiotic prophylaxis (1 g of cefazolin) was given within 1 h before skin incision. In patients with penicillin allergy, other antibiotics were prescribed as appropriate. Intra-operatively, laminar airflow and body exhaust systems were used. There was no routine use of antibiotic-loaded cement or postoperative antibiotics. Postoperative wound management was the same throughout the study period.

Cohort characteristics, occurrence of PJI, and bacteriological data were retrieved. Bacterial type

## 初次全膝關節置換術後人工關節周邊關節感染的細菌學和風險因素：2543例回溯性研究

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引言：全膝關節置換術後人工關節周邊關節感染是一種嚴重併發症。本研究旨在確定一所教學醫院進行初次全膝關節置換術後人工關節周邊關節的風險因素和細菌學特徵。

方法：我們回顧1993年至2013年期間在本院進行的2543例常規初次全膝關節置換術。數據來自醫院管理局臨床數據分析和報告系統、感染控制小組以及關節置換部門資料統計中心。通過單變量分析和多變量邏輯迴歸，找出潛在危險因素與人工關節周邊關節感染之間的相關性。單變量分析亦被用作檢視潛在風險因素與細菌學之間以及潛在風險因素（包括細菌學）與早發性感染之間的相關性。

結果：人工關節周邊關節感染的現患率為1.34%（34例）。早發感染的現患率為0.39%（24例）。在人工關節周邊關節感染的病例中，29.4%為早發性感染。在單變量和多變量分析中，只有類風濕關節炎是人工關節周邊關節感染的重要預測因子。對甲氧西林具耐藥性的金黃色葡萄球菌是最常見致病微生物。潛在危險因素與細菌學之間沒有顯著相關性。由皮膚菌群引起的人工關節周邊關節感染與早發性感染呈正相關但在統計學上並不顯著。

結論：1993年至2013年期間在本院進行常規全膝關節置換術後，人工關節周邊關節感染的現患率為1.34%。類風濕關節炎是人工關節周邊關節感染的重要危險因素。

was defined as infection with skin flora or non-skin flora. Skin flora included methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S aureus* (MRSA), methicillin-susceptible coagulase-negative staphylococci (MSCNS), and methicillin-resistant coagulase-negative staphylococci (MRCNS). Other organisms were considered non-skin flora.

The following potential risk factors for PJI were analysed: age, sex, presence of diabetes, presence of rheumatoid arthritis, and one-stage bilateral TKA. They were examined by univariable analyses and then multivariable logistic regression to identify potential predictors of PJI, while controlling for confounders. We also studied the association of those potential risk factors with bacteriology and with the timing of infection onset; culture-negative PJI was excluded from these analyses. According to a working party convened by the Musculoskeletal Infection Society in 2014,<sup>15</sup> PJI that occurs within 90 days of the index operation is considered early-onset infection, whereas PJI that occurs later is considered late-onset infection.

Both univariable and multivariable logistic regression in this study used the simultaneous entry method, with covariates of age (as a continuous variable) and sex, diabetes, rheumatoid arthritis,

and one-stage bilateral TKA (as dichotomous variables). Outcomes are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The regression model and data fitting were assessed using the Hosmer–Lemeshow goodness-of-fit test, and diabetes and one-stage bilateral TKA were excluded from the final model because of poor goodness-of-fit. For associations between potential risk factors and bacteriology and between potential risk factors and early onset of infection, only univariable analyses were used owing to small numbers of events. Categorical variables were compared with the chi-square test, whereas age was compared with the independent *t* test (two-tailed). Significance was assumed if *P*<0.05. All statistical analyses were conducted using SPSS version 22.0 (IBM Corporation, Armonk [NY], United States).

TABLE 1. Descriptive statistics for potential risk factors according to occurrence of periprosthetic joint infection after primary total knee arthroplasty

Risk factor		PJI occurrence
Sex	Male	10/539 (1.9%)
	Female	24/2004 (1.2%)
Diabetes	Yes	9/484 (1.9%)
	No	25/2034 (1.2%)
Rheumatoid arthritis	Yes	7/222 (3.1%)
	No	27/2287 (1.2%)
One-stage bilateral TKA	Yes	13/1062 (1.2%)
	No	21/1481 (1.4%)

Abbreviations: PJI = periprosthetic joint infection;TKA = total knee arthroplasty

The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

## Results

The incidence of PJI in our series was 1.34% (n=34). The incidence of early-onset infection was 0.39% (n=10) and that of late-onset infection was 0.94% (n=24). Among the cases PJI, 29.4% were early-onset infection. Early-onset infection occurred within a median of 17 days after arthroplasty (interquartile range, 9-32 days). Late-onset infection occurred within a median of 1 year and 8 months after arthroplasty (interquartile range, 7 months to 2 years and 11 months). Fifty-nine percent of infections occurred in the first year of surgery, whereas 74% occurred in the first 2 years.

The mean (standard deviation) age was 69 (9) years, with a range from 21 to 91 years; age followed a normal distribution. Overall, PJI developed in 10 males (1.9%) and 24 females (1.2%). In the one-stage bilateral TKA group, PJI occurred in 13 knees (1.2%). For the single-side TKA group, 21 knees (1.4%) developed PJI. Nine patients with diabetes (1.9%) and 25 patients without diabetes (1.2%) developed PJI. The highest rate of PJI, at 3.1%, was found in patients with rheumatoid arthritis, compared with 1.2% in patients without rheumatoid arthritis. The descriptive data are summarised in Table 1.

The most frequent causative organism was MSSA (26.5%, n=9), followed by MRSA (17.6%, n=6), *Streptococcus* spp (8.8%, n=3), MSCNS (5.9%, n=2), *Escherichia coli* (5.9%, n=2), *Salmonella* (5.9%, n=2), MRCNS (2.9%, n=1) and *Mycobacterium tuberculosis* (2.9%, n=1). The three cases of streptococcal infection comprised two *Streptococcus*

TABLE 2. Association between potential risk factors for periprosthetic joint infection after primary total knee arthroplasty and bacteriology

Risk factor		Organisms of PJI		Pearson chi-square	P value
		Skin flora *†	Non-skin flora †		
Sex	Male	6 (75.0%)	2 (25.0%)	0.181	0.671
	Female	12 (66.7%)	6 (33.3%)		
Diabetes	Yes	5 (71.4%)	2 (28.6%)	0.022	0.639
	No	13 (68.4%)	6 (31.6%)		
Rheumatoid arthritis	Yes	2 (33.3%)	4 (66.7%)	4.719	0.051
	No	16 (80.0%)	4 (20.0%)		
One-stage bilateral TKA	Yes	4 (44.4%)	5 (55.6%)	3.97	0.078
	No	14 (82.4%)	3 (17.6%)		
Age		–	–	–	0.306

Abbreviations: PJI = periprosthetic joint infection;TKA = total knee arthroplasty

\* Methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S aureus*, methicillin-susceptible coagulase-negative staphylococci, and methicillin-resistant coagulase-negative staphylococci were considered skin flora; other organisms were considered non-skin flora. Culture-negative PJI was excluded from this analysis

† Percentages are those of each risk-factor group

*dysgalactiae* infections and one *Streptococcus agalactiae* infection. Culture-negative PJI comprised 23.5% of cases (n=8). Methicillin-resistant strains constituted 39% of all staphylococcal organisms. There was no significant association between the potential risk factors and skin flora infection (Table 2).

Rheumatoid arthritis was a significant risk factor of PJI in the univariable analysis, with an OR of 2.67 (95% CI, 1.15-6.20; P=0.02), as well as in the multivariable analysis, with an OR of 3.12 (CI, 1.29-7.56; P=0.01) [Table 3]. Being male (OR=1.9; P=0.11 in the multivariable analysis) and having diabetes (OR=1.54; P=0.27 in the univariable analysis) were not significantly associated with PJI.

Age (P=0.655), sex (P=0.961), diabetes (P=0.462), and rheumatoid arthritis (P=0.315) were not associated with early-onset infection (Table 4).

Infection caused by skin flora was associated with early-onset infection (P=0.099), but the association was not statistically significant.

### Discussion

In this study, the incidence of PJI after primary TKA was 1.34% and the incidence of early-onset infection was 0.39%. The majority of PJIs (70%) were late-onset infections. The reported incidence of PJI after primary TKA ranges from 1.1% to 2.18%.<sup>16-18</sup> Pulido et al<sup>16</sup> reported the incidence of PJI after TKA to be 1.1%, of which 27% were diagnosed during the first 30 days after arthroplasty, and a majority of 65% were diagnosed in the first year after surgery. In our study, the average time to diagnosis was 431 days after the index surgery (range, 11-1699 days).

Rheumatoid arthritis was a significant risk factor for PJI after primary TKA. This finding is in

TABLE 3. Results of univariable and multivariable analyses of potential risk factors for periprosthetic joint infection after primary total knee arthroplasty

Risk factor	Univariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Rheumatoid arthritis	2.67	1.15-6.20	0.02	3.12	1.29-7.56	0.01
Age	1.01	0.98-1.05	0.56	1.00	0.97-1.04	0.69
Male sex	1.56	0.741-3.28	0.24	1.90	0.88-4.15	0.11
Diabetes*	1.54	0.72-3.32	0.27	-	-	-
One-stage bilateral TKA*	0.86	0.43-1.73	0.68	-	-	-

Abbreviations: OR = odds ratio; CI = confidence interval; TKA = total knee arthroplasty

\* Excluded from the multivariable regression model because of poor goodness-of-fit

TABLE 4. Association between potential risk factors for periprosthetic joint infection after primary total knee arthroplasty and onset of infection

Risk factor		Onset of infection		Pearson chi-square	P value
		Early*	Late*		
Sex	Male	3 (30.0%)	7 (70.0%)	0.002	0.961
	Female	7 (29.2%)	17 (70.8%)		
Diabetes	Yes	2 (22.2%)	7 (77.8%)	0.305	0.462
	No	8 (32.0%)	17 (68.0%)		
Rheumatoid arthritis	Yes	1 (14.3%)	6 (85.7%)	0.971	0.315
	No	9 (33.3%)	18 (66.7%)		
One-stage bilateral TKA	Yes	2 (15.4%)	11 (84.6%)	1.995	0.153
	No	8 (38.1%)	13 (61.9%)		
Skin flora infection	Skin flora†	9 (50.0%)	9 (50.0%)	3.291	0.099
	Non-skin flora	1 (12.5%)	7 (87.5%)		
Age		-	-	-	0.655

Abbreviation: TKA = total knee arthroplasty

\* Percentages are those of each risk-factor group

† Methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S aureus*, methicillin-susceptible coagulase-negative staphylococci, and methicillin-resistant coagulase-negative staphylococci were considered skin flora; other organisms were considered non-skin flora. Culture-negative periprosthetic joint infection was excluded from this analysis

keeping with the current literature.<sup>6,8,11</sup> Although various authors have found male sex to be a risk factor for PJI,<sup>4,19,20</sup> the association was not significant in this study. The OR of 1.9 may be of clinical importance but not significant as a result of the small number of PJIs and inadequate statistical power. The correlation between age and PJI has been a matter of controversy, with some reports mentioning young age as a risk factor for PJI<sup>4,21</sup> and some otherwise.<sup>22</sup> In our study, age was not associated with PJI occurrence. For one-stage bilateral TKA, age has been a controversial risk factor for PJI. Some studies<sup>16,23</sup> have suggested that one-stage bilateral TKA is associated with an increased risk of superficial and deep infection. Hussain et al<sup>24</sup> nonetheless reported a similar infection rate between one- and two-stage bilateral TKA. Our study did not find an association between one-stage bilateral TKA and PJI occurrence.

The local bacteriological pattern for PJI was comparable to that reported in the literature.<sup>4,16</sup> In our study, skin flora and gram-positive bacteria were the most commonly isolated organisms, followed by gram-negative bacteria such as *Escherichia coli* and *Salmonella*. Coagulase-negative staphylococci were the most common causative organism in one study.<sup>4</sup> In contrast, in our series, *S aureus* was the most common causative organism, particularly methicillin-sensitive strains. Methicillin-resistant strains were less common in our series, constituting 39% of all staphylococcal organisms.

Other authors have reported that male sex is a risk factor for PJI, which may be related to a sex difference in immune response to pathogenic bacteria. Studies<sup>6</sup> have shown that males (compared with females) have a significantly higher likelihood of being a persistent *S aureus* carrier. However, our study did not support male sex as a risk factor for infection with skin flora. With regard to onset of infection, PJI caused by skin flora was positively associated with early-onset infection, although the association did not reach statistical significance ( $P=0.099$ ). Direct inoculation and spread from contiguous foci of infection are more common in early-onset infection caused by wound complications and local soft-tissue conditions. In contrast, distant foci of infection, such as in bacteraemia, play a more important role in late-onset infection. Therefore, in early-onset periprosthetic joint infection with negative cultures, an empirical antibiotic regimen may provide adequate coverage against skin flora organisms.

Fan et al<sup>20</sup> reported 479 TKAs and rates of 1.9% for superficial wound infection, 0.2% for early deep infection ( $n=1$ ), and 0.6% for late deep infection ( $n=2$ ). Methicillin-sensitive *S aureus* and coagulase-negative staphylococci were causative organisms. Lee et al<sup>25</sup> reviewed 1133 primary TKAs and found a 0.71% incidence of PJI. The most common causative

organisms in descending order were methicillin-sensitive *S aureus*, coagulase-negative staphylococci, methicillin-resistant *S aureus*, and *Pseudomonas aeruginosa*. This finding is in keeping with our data. Among risk factors identified by Lee et al<sup>25</sup> were young age, diabetes, anaemia, thyroid disease, heart disease, lung disease, and long operating time. However, the researchers identified limitations of having only a small number of patients with infection ( $n=8$ ) and insufficient power for analysis. In addition, multivariable analysis should have been performed to account for the effect of confounders among the multiple risk factors. They also reported the limitation that the mean follow-up duration was only 2 years. A short follow-up period may underestimate the occurrence of late-onset infection.

Our study has several limitations. The number of PJI-positive cases was small and thus subgroup analysis was limited. This study included subjects treated at a single centre in Hong Kong; multicentre studies may improve the representativeness of local data. In addition, perioperative management for elective TKA has evolved over the past 20 years, including the introduction of an MRSA-screening programme in 2011. In the screening programme, a nasal swab is taken from all elective joint-replacement patients. Patients with a positive result are prescribed 5 days of decolonisation therapy including a daily chlorhexidine bath. Furthermore, intravenous vancomycin is now administered for prophylaxis instead of cefazolin.<sup>26</sup>

There are many potential risk factors for PJI documented in the literature. Nonetheless, only a limited number were included in this study, most of which are not be modifiable. Thus, it may not provide the necessary guidance for preoperative optimisation. Furthermore, the exclusion of some potential risk factors may have led to inadequate control for potential confounding factors. Inclusion of more risk factors with better characterisation is needed to provide a more comprehensive understanding and to better account for the confounding effect of other variables.

## Conclusion

The incidence of PJI after elective primary TKA in our institution over two decades from 1993 to 2013 was 1.34%. Rheumatoid arthritis was a significant risk factor for PJI in this series. In the early-onset infection group, PJI was caused by skin flora, but this was not statistically significant. It is hoped that this study has updated the local data for PJI after primary TKA and serves as a model for future related studies.

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## Declaration

The authors have no conflicts of interest to disclose.

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