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Original Article

The incidence rate, trend and microbiological aetiology of prosthetic joint infection after total knee arthroplasty: A 13 years' experience from a tertiary medical center in Taiwan

Fu-Der Wang [a,b,*,1], Yu-Ping Wang [a,1], Cheng-Fong Chen [c,d], Hsin-Pai Chen [a,b]

[a] *Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[b] *School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[c] *Department of Orthopedics and Traumatology, Taipei Veterans General Hospital, Taipei, Taiwan*
[d] *Department of Orthopedics, School of Medicine, National Yang-Ming University, Taipei, Taiwan*

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KEYWORDS
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Abstract *Background/purpose:* Total knee arthroplasty (TKA) improves the patient's quality of life by relieving pain, correcting the deformity, and helping the patient resume normal activities. However, post-TKA prosthetic joint infection leads to implant failure, is difficult to treat, and causes a significant burden both economically and health-wise. Therefore, an understanding of the current trends in this infection and microbiology data is essential for preventing and treating it.
Methods: A retrospective study was conducted on 10,768 patients who underwent primary TKA at Taipei Veterans General Hospital, Taiwan, from 2002 to 2014. The incidence of post-TKA prosthetic joint infection in different time periods was investigated, and microbiological results in early- (<3 months post-TKA) and delay-onset prosthetic joint infection were analyzed.
Results: The 2 years incidence of post-TKA prosthetic joint infection was 1.93% (2002–2006), 1.05% (2007–2010), and 0.76% (2011–2014). The incidence of post-TKA prosthetic joint infection decreased significantly from 2002 to 2014. Although *Staphylococcus* species was most commonly isolated, a significantly higher proportion of gram-negative bacteria were isolated

* Correspondence author. Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, 201 Shih-Pai Road, Sec. 2, Taipei 11247, Taiwan. Fax: +886 2 2873 5656.
E-mail address: fdwang@vghtpe.gov.tw (F.-D. Wang).
[1] Fu-Der Wang and Yu-Ping Wang equally contributed to the work.

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from early-onset compared with delay-onset post-TKA prosthetic joint infection patients: 9/29 (31.0%) versus 13/100 (13%); $p = 0.023$.
Conclusions: The results showed that the risk of post-TKA prosthetic joint infection is decreasing. Microbiology results showed that early-onset post-TKA prosthetic joint infection is associated with a higher risk of gram-negative bacterial infection. Physicians should be aware of this risk in order to correctly select empirical agents.

Introduction

Total knee arthroplasty (TKA) is a major life-enhancing surgery that relieves pain, recovers joint function, and improves the patient's quality of life. Previous studies have reported increased numbers of primary TKAs in the United States,[1] European countries,[2] and Taiwan over time.[3] Although most TKAs are expected to provide good joint function, some patients may suffer from implant failure. Post-TKA prosthetic joint infection is one of the most common causes of implant failure,[4] causing large economic and health impacts.

Many new strategies to prevent post-TKA prosthetic joint infection have been developed, such as preoperative skin cleaning, prophylactic antibiotics, antibiotic-loaded bone cement, and double-gloving.[5,6] Therefore, it is expected that the rate of post-TKA prosthetic joint infection should decrease. However, the trends in the incidence of post-TKA prosthetic joint infection are still unclear. The 2001–2009 Nationwide Inpatient Sample of the United States and the Nordic Arthroplasty Register Association dataset showed an increase in the annual rate of post-TKA prosthetic joint infection over time.[7] On the other hand, a small population-based study (Rochester Epidemiology Project) on 7367 prosthetic joints showed no change in the rate of infection from 1969 to 2007.[8]

Microbiology studies revealed that gram-positive bacteria are more prevalent than gram-negative bacteria in post-TKA prosthetic joint infection.[9–11] *Staphylococcus* species accounted for around 40%–60% of the isolates. Gram-negative bacteria were involved in <15% of all post-TKA prosthetic joint infections in most reports and required more complicated and longer treatment.[12]

To prevent and treat post-TKA prosthetic joint infection, it is important to understand the current trends in this infection and microbiology data. This study determined the incidence of post-TKA prosthetic joint infection in different time periods and the microbiological etiology of this infection.

Methods

We conducted a retrospective study at Taipei Veterans General Hospital, a 2900-bed tertiary medical center in Taiwan. Patients ($n = 10{,}768$) older than 18 years who underwent primary TKA from 2002 to 2014 were included in the study. A post-TKA prosthetic joint infection event was defined as an infection that required surgical intervention, including infection-related arthrotomy and infection-related revision arthroplasty. Infection as the cause of revision or arthrotomy was determined and reported by the surgeon based on the preoperative clinical manifestations and intraoperative evaluation. Infections occurring <3 months post-TKA were defined as early-onset infections, whereas those occurring >3 months post-TKA were defined as delay-onset infections. The medical records of patients with post-TKA prosthetic joint infection were reviewed and summarized by at least two infectious disease specialists. The patients were observed until infection-related arthrotomy and debridement, infection-related first revision arthroplasty, or December 31, 2017.

The causative organism(s) was determined to be a pathogen if isolated from intraoperative specimens. Identification and susceptibility testing of isolates were performed with standard microbiological techniques and in accordance with methods approved by the Clinical and Laboratory Standards Institute.[13]

The incidence rates were calculated and plotted by time from primary TKA to surgical intervention for post-TKA prosthetic joint infection (3 months, 6 months, 1 year, and 2 years). For 5 years incidence, because of an insufficient follow-up period, we included only those patients who underwent TKA during 2002–2012. Log-linear regression using the primary TKA year as a continuous independent factor was used to investigate overall linear trends between 2002 and 2014. The study population was divided into groups by primary surgery year range (2002–2006, 2007–2010, and 2011–2014), gender, age (<65, 66–70, 71–75, and >75 years), and diagnosis. The cumulative incidence was calculated and plotted, and the log-rank test was used to compare the cumulative incidence between groups. In addition, descriptive statistics were used to summarize the data. Descriptive analyses were based on percentages and frequencies for categorical variables and on means and standard deviations for continuous variables. $p < 0.05$ was considered statistically significant. SPSS Statistics ver. 24.0 was used for analysis.

Results

This retrospective study was conducted on 10,768 patients, of which 7241 (67.2%) were women and 3527 (32.8%) were men. The median age of the patients was 73 years. The most common cause of TKA was found to be osteoarthritis, accounting for 10,398 (96.6%) patients; 216 patients (2.0%) required TKA due to rheumatoid arthritis,

whereas 154 patients (1.4%) underwent TKA due to various other diagnoses. Table 1 shows the basic characteristic of the patients who underwent TKA in our hospital during 2002–2014.

Of the 10,768 patients, 178 (1.65%) required surgical intervention due to post-TKA prosthetic joint infection during the follow-up period. Most of these infections (128 of 178, 72%) occurred within 2 years post-TKA. The incidence of post-TKA prosthetic joint infection 3 months, 6 months, 1 year, 2 years, and 5 years (2002–2012) after surgery was 0.41% (44 patients), 0.54% (58 patients), 0.79% (85 patients), 1.19% (128 patients), and 1.54% (133 patients), respectively; 16 patients required surgical intervention due to post-TKA prosthetic joint infection 5 years after surgery. Fig. 1 shows the trends in the incidence of post-TKA prosthetic joint infection 3 months, 6 months, 1 year, and 2 years after surgery. We observed a significant decrease in the incidence of post-TKA prosthetic joint infection over time in the 3 months, 6 months, 1 year, and 2 years follow-up periods. The 2 years incidence of post-TKA prosthetic joint infection in the three time periods was 1.93% (2002–2006), 1.05% (2007–2010), and 0.76% (2011–2014).

Fig. 2 shows the cumulative incidence of post-TKA prosthetic joint infection in patients separated by age, sex, diagnosis, and three time periods. The cumulative incidence of post-TKA prosthetic joint infection for the youngest age group (<65 years) was found to be higher compared with other age groups ($p < 0.001$), and men were associated with a higher infection rate than women ($p < 0.001$). The cumulative incidence of post-TKA prosthetic joint infection was significantly lower in 2007–2010 compared with 2002–2006 and was the lowest in 2011–2014 ($p < 0.001$).

Of the 178 patients who required surgical intervention due to post-TKA prosthetic joint infection during the follow-up period, at least one microorganism was isolated from 129 patients, more than two microorganisms were isolated from 9 patients, whereas 49 grew nothing from culture. Gram-positive bacteria accounted for 60.1% ($n = 107$) of the 178 patients with post-TKA prosthetic joint infection. *Staphylococcus aureus* was the most common pathogen isolated ($n = 55$, 30.9%: 39 patients with methicillin-susceptible *S. aureus* and 16 patients with methicillin-resistant *S. aureus*), followed by coagulase-negative *Staphylococcus* species ($n = 23$, 12.9%), *Streptococcus* species ($n = 20$, or 11.2%), and *Enterococcus* species ($n = 9$, 5.1%). Gram-negative bacteria were isolated from 22 patients (12.4%); the most common species were *Enterobacteriaceae* ($n = 13$, 7.3%) and *Pseudomonas aeruginosa* ($n = 5$, 2.8%). Anaerobes were isolated from 8 patients (5.5%). Only 2 patients (1.1%) showed *Candida* species isolates. Table 2 lists the details of microbiology

Table 1 Basic characteristics for the patients received total knee arthroplasty.

Characteristic	No. (%)
No. of patients	10768 (100)
Age (median)	73
<65	2357 (21.9)
66–70	4397 (40.8)
71–75	2228 (20.7)
>76	1786 (16.6)
Gender	
Men	3527 (32.8)
Women	7241 (67.2)
Reason of arthroplasty	
Osteoarthritis	10398 (96.6)
Rheumatoid arthritis	216 (2.0)
Other diagnosis	154 (1.4)
Time period	
2002–2006	3060 (28.4)
2007–2010	3520 (32.7)
2011–2014	4188 (38.9)

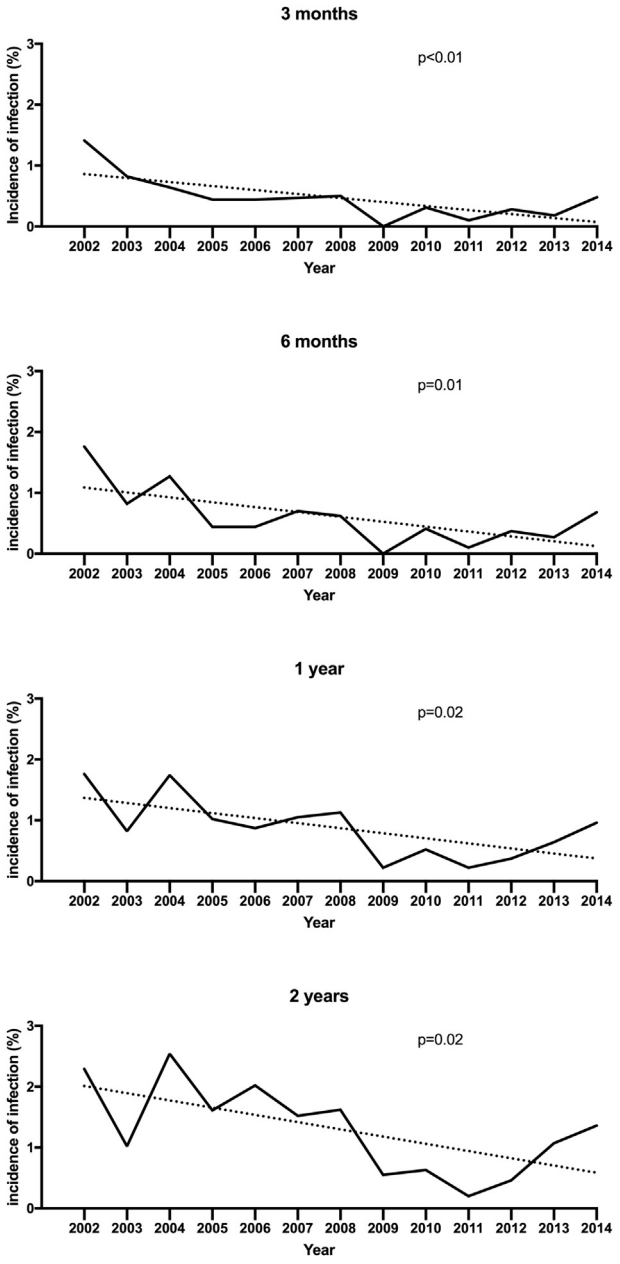

Figure 1. Incidence and regression line within 3 months, 6 months, 1 year and 2 years of post total knee arthroplasty prosthetic joint infection after total knee arthroplasty.

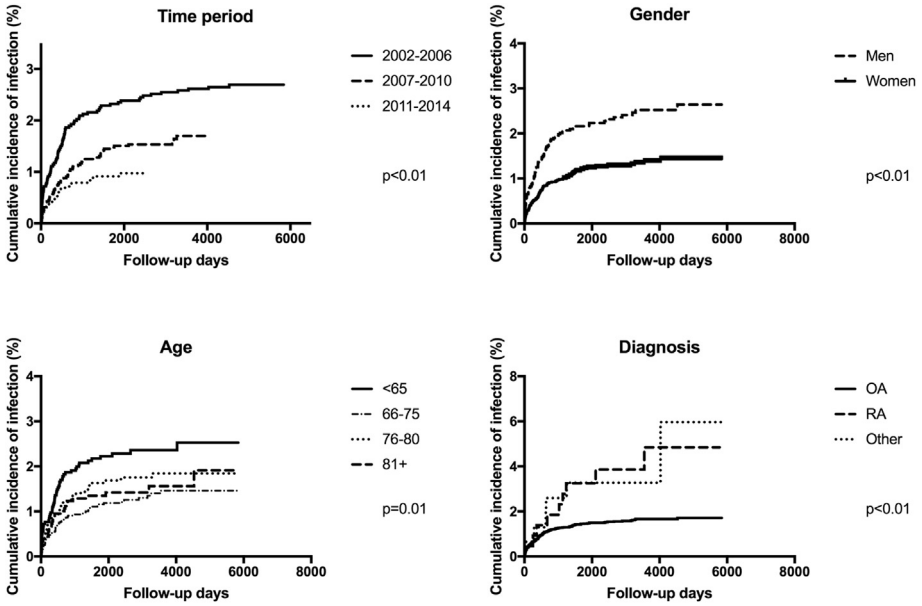

Figure 2. Cumulative incidence of post total knee arthroplasty prosthetic joint infection in different age, sex, and time period.

Table 2 Microorganisms isolated from patients with post total knee arthroplasty prosthetic knee joint infection.

Microorganism	Isolate No. (%)
Gram-positive bacteria	107 (60.1)
Staphylococcus aureus	55 (30.9)
Methicillin-susceptible	39 (21.9)
Methicillin-resistant	16 (9.0)
Coagulase-negative *staphylococcus* species	23 (12.9)
Streptococcus species	20 (11.2)
Enterococcus species	9 (5.1)
Gram-negative bacteria	22 (12.3)
Enterobacteriaceae	13 (7.3)
Escherichia coli	3 (1.7)
Klebsiella pneumoniae	4 (2.2)
Enterobacter cloacae	2 (1.1)
Citrobacter freundii	1 (0.6)
Proteus mirabilis	1 (0.6)
Salmonella group D	2 (1.1)
Pseudomonas aeruginosa	5 (2.8)
Acinetobacter baumannii	1 (0.6)
Stenotrophomonas maltophilia	1 (0.6)
Haemophilus parainfluenzae	1 (0.6)
Brevundimonas diminuta	1 (0.6)
Anaerobes	8 (4.5)
Propionibacterium acnes	4 (2.2)
Peptostreptococcus species	2 (1.1)
Unidentified anaerobic GPB	2 (1.1)
Candida species	2 (1.1)

results for culture-positive post-TKA prosthetic joint infection. Although we noted a decreasing incidence of post-TKA prosthetic joint infection over time, the *Staphylococcus* species was still the most common species isolated. In 129 culture-positive patients, *S. aureus is* still the most common pathogen isolated in both early- and delay-onset post-TKA prosthetic joint infection patients: 15/29 (51.7%) versus 30/100 (39%); $p = 0.221$. However, a significantly higher proportion of gram-negative bacteria were cultured from early-onset compared with delay-onset post-TKA prosthetic joint infection patients [9/29 (31.0%) versus 13/100 (13%); $p = 0.023$]. Coagulase-negative *Staphylococcus* species were significantly less commonly isolated from early-onset infection compared with delay-onset post-TKA prosthetic joint infection patients [1/29 (3.4%) versus 22/100 (22%); $p = 0.022$]. *Streptococcus* species tended to be less isolated from early-onset compared with delay-onset post-TKA prosthetic joint infection patients, but no statistical significance could be found [2/29 (6.9%) versus 15/100 (15%); $p = 0.256$]. Fig. 3 shows the proportion of microorganisms isolated from the patients in three time periods, and Fig. 4 shows the proportion of microorganisms isolated from early- and delay-onset post-TKA prosthetic joint infection patients.

Discussion

The results of our study suggested a decreased risk of post-TKA prosthetic joint infection over time that required surgical intervention. The microbiological data showed that gram-positive bacteria still account for most of the post-TKA prosthetic joint infections; in this study, *S. aureus* was the most common species isolated. Early- and delay-onset post-TKA prosthetic joint infection had different microbiological etiologies, and gram-negative bacteria were more prominent in early-onset compared with delay-onset post-TKA prosthetic joint infection.

Trends in the rate of infection are also an important issue. The rate of post-TKA prosthetic joint infection reported by previous studies ranged from 0.4% to 2.2%.[7,11,14,15] Tsaras et al. followed up 7367 patients with prosthetic joints from 1969 to 2007 and found no change in

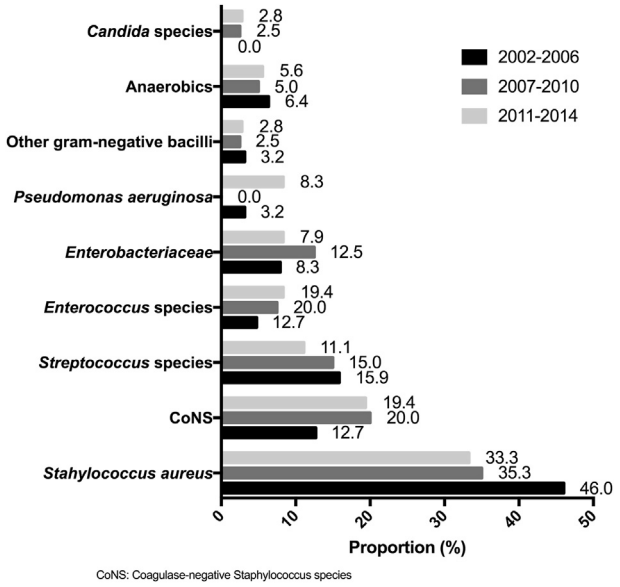

Figure 3. Proportion of microorganism isolated from patients with post total knee arthroplasty prosthetic joint infection in the three time periods.

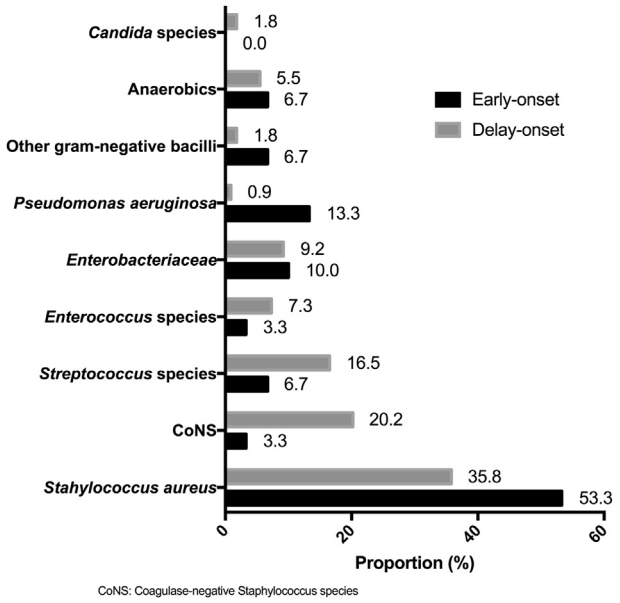

Figure 4. Proportion of microorganisms isolated from patients with early- and delay-onset post total knee arthroplasty prosthetic joint infection.

the rate of infection.[16] Recently, Kurtz et al. found a slightly but still significant increase in rate of post-TKA prosthetic joint infection from 2001 to 2009 (2.05%–2.18%, $p = 0.003$).[7] In a large National Joint Registry from 2003 to 2014 for England and Wales, Lenguerrand et al.[14] found a rise in the prevalence of revision arthroplasty due to post-TKA periprosthetic joint infection in the 3 months following primary and revision TKA (time trend $p < 0.0001$) from 2005 to 2013. The precise cause of the increase in infection in these studies is unclear.

To our knowledge, our study is the first to reveal a decreasing rate of post-TKA prosthetic joint infection over time. We observed a significant trend in the decrease in the infection rate from 2002 to 2014. Compared with other studies, in this study, we presented clearly distinct infection rates in different time periods. Optimized timing for prophylactic antibiotics, antibiotic-loaded bone cement, and double-gloving might contribute to an improvement in the infection rate. The timing of prophylactic cefazolin was requested to be administrated around 30 min before surgery, and postoperative prophylaxis should be discontinued within 24 h. These strategies were applied in our hospital during 2006–2008. The 2 years infection rate after total knee arthroplasty were decreased from 1.90% (2002–2005, before these strategies applied) to 0.71% (2009–2014, after these strategies applied). However, it is difficult to evaluate the accurate effect of each strategy in our retrospective design because the medical records in these strategies were incomplete, and multiple strategies were applied in the period.

Previous reports still revealed *S. aureus* is the most common species isolated.[10,17–19] However, increasing gram-negative bacterial infections, especially multidrug-resistant gram-negative bacilli were reported.[18,20] According to current local and international guidelines,[21,22] gram-positive coverage agent such as cefazolin and vancomycin is recommended for prophylaxis antibiotics before the arthroplasty. The use of prophylaxis antibiotics before surgery may lead to the shift in microbiological aetiology.[23] In our study, we did not observe the change of microbiology results over time, but significant higher proportion of gram-negative bacterial infections in early onset infection was found. Prophylaxis cefazolin and vancomycin-loaded bone cement were used commonly in our hospital setting, these strategies might contribute to increased proportion of early onset gram-negative bacterial infections. However, the overuse of prophylaxis antibiotics may increase risk for infection caused by multidrug resistant pathogens and alternation of intestinal flora.[24,25] Identifying risk factors for gram-negative bacterial infections is important for reassessing current antibiotics prophylaxis strategies.

Taipei Veterans General Hospital is a large tertiary medical center in Taiwan, the hospital performed more than 500 TKAs every year since 2002. As a single center study, strength of our study is relatively large sample size and long follow-up period. We obtained the medical record and microbiology result, to make our diagnosis more accurate. We presented infection incidence rate and microbiological result in different time period clearly, which provide physicians more accurate information.

One limitation of our study was its retrospective, descriptive and single center design. Another limitation was that we did not include patients who only underwent conservative treatment. However, as it is difficult to distinguish between a superficial infection and a true deep prosthetic joint infection in conservative treatment, the rate of infection might be overestimated if these patients are included. The third limitation was that we used conventional culture method to identify pathogen, but some of the pathogen can only be detected by specific culture conditions or molecular biology.[26]

The results of our study suggested that it is possible to decrease the rate of post-TKA prosthetic joint infection. Our microbiology results showed a discrepancy between early- and delay-onset post-TKA prosthetic joint infections. Further studies to identify risk factors and formulate new strategies to prevent post-TKA prosthetic joint infection are warranted. In addition, physicians should be aware of the risk of early-onset gram-negative bacterial post-TKA prosthetic joint infection for correctly selecting prophylactic and empirical agents.

Conflicts of interest

The authors declare no conflict of interest.

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