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Microbiology of Hip and Knee Periprosthetic Joint Infections: A Database Study

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Abstract

Objectives.—Knowledge of the microbiologic etiology of periprosthetic joint infection (PJI) is essential to its management. Contemporary literature from the United States on this topic is lacking. This study aimed to identify the most common microorganisms associated with types of arthroplasty, the timing of infection, and clues to polymicrobial infection.

Methods.—We performed an analytical cross-sectional study of patients 18 years of age or older with hip or knee PJI diagnosed at our institution between 2010 and 2019. PJI was defined using the criteria adapted from the Musculoskeletal Infection Society. Cases included PJI associated with primary or revision arthroplasty and arthroplasty performed at our institution or elsewhere.

Results.—A total of 2,067 episodes of PJI in 1,651 patients were included. Monomicrobial infections represented 70% of episodes (n=1,448), with 25% being polymicrobial (n=508) and the rest (5%, n=111) being culture-negative. The most common group causing PJI was coagulase-negative *Staphylococcus* species (other than *S. lugdunensis*) (37%, n=761). The distribution of most common organisms was similar regardless of arthroplasty type. *S. aureus* complex, Gram-

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Author Contributions

Dr. Tai and Dr. Tande: Conceptualization, methodology, validation, formal analysis, investigation, writing the manuscript.

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negative bacteria, and anaerobic bacteria (other than *Cutibacterium* species) were more likely to be isolated in the first year following index arthroplasty compared to other organisms (OR 1.7, 95% CI 1.4–2.2; OR 1.5, 95% CI 1.1–2.0; OR 1.5, 95% CI 1.0–2.2, respectively). The proportion of culture-negative PJI was higher in primary than revision arthroplasty (6.5% versus 3%, $p=0.0005$). The presence of a sinus tract increased the probability of isolation of more than one microorganism by almost three-fold (OR 2.6, 95% CI 2.0–3.3).

Conclusions.—Joint age, presence of a sinus tract, and revision arthroplasties influenced PJI microbiology.

Keywords

most common; hip PJI; knee PJI; microbiologic etiology; periprosthetic joint infection

Introduction

Hip and knee arthroplasties are standard procedures projected to increase in incidence over time (1). Consequently, the number of periprosthetic joint infections (PJIs) is also projected to increase (2, 3). Accurate knowledge of the microbiologic etiology of PJI is critical to choosing appropriate antimicrobials and has prognostic implications. Studies on this topic are based on cohort data from the 1990s to early 2000s, small sample sizes, or non-United States data (4–6). Extensive, up-to-date studies from the United States are lacking. We hypothesized that recent advances in surgical practices, infection prevention and control, and culture techniques might have altered the microbiologic etiology of PJI (7). More importantly, the definition of PJI applied varied widely before 2010, until societies and experts converged on criteria to diagnose PJI (8). The definition has varied slightly with each iteration from different groups this past decade (9, 10). With this background, we sought to update information on the microbiology of PJI using a large sample size.

The goal was to update knowledge on the microbiologic etiology of hip and knee PJI using a large institutional database. Specifically, the most common genera and species involved were defined. In addition, potential differences between monomicrobial and polymicrobial infections, including clinical clues to the presence of polymicrobial infection and differences in microbiology based on arthroplasty type and joint age, were examined.

Methods

An analytical cross-sectional study of patients 18 years of age or older with hip or knee PJI diagnosed between 2010 and 2019 at Mayo Clinic in Rochester, Minnesota, was performed. The Mayo Clinic Total Joint Registry (TJR) and its accompanying PJI database were queried. The TJR captured information on arthroplasties performed at Mayo Clinic, including those complicated by infection. The PJI database registered all cases of PJI diagnosed and treated at Mayo Clinic (11, 12). Cases included PJIs associated with total hip arthroplasty, hip hemiarthroplasty, total knee arthroplasty, or unicompartmental knee arthroplasty performed either at the Mayo Clinic (internal cases) or other institutions (referred cases). Types of arthroplasties were primary and revision arthroplasties. This study

was deemed exempt by the Mayo Clinic Institutional Review Board. Participant consents were acquired through the Minnesota Research Authorization process.

PJI was defined using criteria adapted from Musculoskeletal Infection Society, specifically (1) two positive periprosthetic specimen cultures with at least one matching organism, or (2) the presence of a sinus tract communicating with the joint, or (3) four of the following: (a) serum C-reactive protein (CRP) of >100 mg/L and erythrocyte sedimentation rate (ESR) of >30 mm/hr, (b) synovial fluid white blood cell (WBC) count of >10,000 cells/ μ L, (c) synovial fluid polymorphonuclear neutrophil (PMN) percentage of >90%, (d) histological analysis of periprosthetic tissue with >5 PMNs per high power field, (e) organism(s) identified from a single positive periprosthetic specimen.

The databases collected data including, but not limited to, sex, joint affected, presence of a sinus tract, number of cultures, dates of surgery, and diagnosis of infection. Microorganisms were identified based on growth from one or more synovial fluid or periprosthetic tissue cultures. All positive single bacterial cultures were included to prevent subjectivity and bias. Timing of infection was categorized as early postoperative if infection occurred within 90 days of most recent surgery, delayed if between 91–365 days, and late if more than 365 days, as traditionally established (13–15). Infections were classified as monomicrobial, polymicrobial, or culture-negative. Polymicrobial infection was defined as the isolation of two or more distinct species in culture, excluding differences in antimicrobial susceptibility profiles.

Culture techniques.

Periprosthetic tissues were homogenized in brain heart infusion broth using a Seward Stomacher 80 Biomaster (Seward Inc., Port St. Lucie, FL). From 2010 to March 2016, homogenates were inoculated onto sheep blood and chocolate agar, incubated aerobically at 35°C in 5% CO₂ for five days, and onto CDC anaerobic blood agar and into a prereduced thioglycollate broth, incubated anaerobically for 14 days. From April 2016 through 2019, homogenates were inoculated into blood culture bottles (BD BACTEC™ Plus Aerobic/F medium and BD BACTEC™ Lytic/10 Anaerobic/F medium) and incubated on the BACTEC 9240/FX instruments (BD Diagnostic Systems) for 14 days. Synovial fluid of >1 mL volume was inoculated into BD BACTEC™ Peds/F blood culture bottle and incubated on BACTEC 9240/FX instruments for five days (January 2010 to April 2019). From May through December 2019, synovial fluid volume of >2 ml was inoculated into BD BACTEC™ Plus Aerobic/F medium and BD BACTEC™ Lytic/10 Anaerobic/F medium and incubated on the BACTEC FX instruments for 14 days. For volumes less than stipulated, conventional plate and broth culture methods were used. Explanted prosthetic joints were sonicated and vortexed in 400 mL of Ringer's solution. The solution was centrifuged and the concentrated specimen plated onto solid media (16, 17). BD BACTEC™ MGIT™ broth and BD™ Middlebrook 7H10 agar were used for mycobacterial cultures. Inhibitory mold agar and brain-heart infusion agar with chloramphenicol, gentamicin, \pm cycloheximide were used for fungal cultures.

Statistical analysis.

Frequency counts and percentages were used for categorical variables, while medians [interquartile ranges (IQRs)] were used for continuous variables. Comparisons of groups were made using Chi-square or Mann-Whitney U test, where applicable. Missing data on patient characteristics were removed from the analysis of that variable. Statistical analyses were performed using BlueSky (BlueSky Statistics, Los Angeles CA) and MedCalc for Windows, version 19.5.1 (MedCalc Software, Ostend, Belgium). *P* values of <.05 were considered significant.

Results

Patient characteristics.

There were 2,067 episodes of PJI in 1,651 patients diagnosed at Mayo Clinic between 2010–2019. The majority was male (57%, n=1170). The median patient age of the cohort was 67 years (IQR 60–75). Each episode had a median of four aerobic and anaerobic bacterial cultures performed (range 1–13). Primary arthroplasties represented 67% (n=1,382), with the rest being revision arthroplasties (33%, n=685). There were 653 primary and 252 revision hip arthroplasties, and 729 primary and 433 revision knee arthroplasties. PJI involving referred cases comprised 52% of episodes (n=1,069), with 48% being internal cases (n=998). The median time from surgery to infection (joint age) was 789 days (IQR 139–2,392). Half of the infections involving internal cases were late infections (n=494), with 37% being early postoperative infections (n=365). In contrast, most referred cases were late infections (77%, n=826), with early postoperative infections constituting only 7% (n=77). Sinus tracts were present in 17% of PJIs (n=346).

Overall, a majority of PJIs was monomicrobial (70%, n=1,448), with 25% being polymicrobial (n=508) and the rest (5%, n=111) being culture-negative (Table 1). Polymicrobial PJI was associated with lower synovial WBC counts (p=.007), a higher proportion of hip PJI (p<.0001), and a higher frequency of sinus tracts (p<.0001) when compared to monomicrobial PJI. Lower WBC counts and the presence of sinus tracts may reflect the chronicity of polymicrobial infection. Those with culture-negative PJI had lower synovial WBC counts compared to culture-positive PJIs (p=.003). Early postoperative knee PJIs were more likely to be polymicrobial than late knee PJIs (OR 2.4, 95% confidence interval [CI] 1.6–3.3). Hip PJIs were polymicrobial in 30% of cases without significant differences in timing from arthroplasty (early 32%, delayed 35%, late 27%; p=.23).

Overview of microbiology.

The most common genus causing PJI was *Staphylococcus* (Table 2). The proportion of microorganisms was similar whether PJIs were associated with hip or knee arthroplasties, primary or revision arthroplasties, or internal or referred cases. The proportion of culture-negative PJI was higher in primary than revision arthroplasties (6.5% versus 3%, p=.0005). *S. aureus* complex was more likely to be isolated in early postoperative compared to late infections (OR 1.7, 95% CI 1.4–2.2). This remained true for all types of arthroplasties except revision arthroplasties in which *S. aureus* was equally likely in all periods. There were no differences between the timing of infection and coagulase-negative staphylococcal

PJI regardless of arthroplasty type or location of the procedure. Streptococci were more likely to be present in delayed and late than early postoperative infections (OR 2.1, 95% CI 1.4–3.0). Gram-negative and anaerobic organisms (other than *Cutibacterium* species) were more common in early or delayed compared with late periods (OR 1.5, 95% CI 1.1–2.0; OR 1.5, 95% CI 1.0–2.2, respectively).

Monomicrobial and polymicrobial infections.

Monomicrobial infections followed the pattern of the overall distribution. The only exception was *Cutibacterium* species which had a bimodal pattern, being more common in early and late than delayed infections (early 9%, delayed 3%, late 6%; $p=.02$ for any difference). 97% of polymicrobial infections involved at least one Gram-positive organism ($n=491$). The presence of a sinus tract increased the probability of polymicrobial infection by almost three-fold (OR 2.6, 95% CI 2.0–3.3) and increased the probability of Gram-negative and anaerobic infections (other than *Cutibacterium* species) by more than two-fold (OR 2.2, 95% CI 1.6–3.0; OR 2.3, 95% CI 1.4–3.9). Even in the absence of a sinus tract, Gram-negative and anaerobic organisms were more than three times more likely to be part of a polymicrobial than monomicrobial infection when compared to Gram-positive organisms (OR 3.5, 95% CI 2.5–4.9; OR 3.2, 95% CI 2.5–4.4). Fungi and mycobacteria were also more likely to be isolated with other microorganisms than alone (OR 3.2, 95% CI 2.0–5.4; OR 12.3, 95% CI 2.7–56.3).

Discussion

This study is one of the largest studies exploring the microbiology of hip and knee PJI. *S. aureus* complex and coagulase-negative *Staphylococcus* species have been reported as the most common pathogens causing PJI. In 2019, a Spanish study found that coagulase-negative staphylococci were more common than *S. aureus* complex, while a study from France published in the same year found otherwise (14, 15). In this single-center study, coagulase-negative staphylococci outpaced *S. aureus* complex as the overall causes of PJI. Our findings challenge the notion that coagulase-negative staphylococci are more common in late infections as they were equally likely in early and delayed-onset infections. As reported in prior studies, *S. aureus* complex was pervasive in early and delayed postoperative infections. *Cutibacterium* species are low-virulence anaerobic organisms and have been considered to be more common in late infections (18); however, we found that these organisms did present in the early period as monomicrobial infections.

We explored associations of type of arthroplasty and joint age with the microbiology of PJI. The analysis of primary *versus* revision arthroplasties demonstrated a similar distribution of microorganisms. However, there was a higher proportion of culture-negative infections with primary arthroplasties. It could be related to the use of blood culture bottles for periprosthetic tissue culture. There were 4% more cultures performed using blood culture bottles in the revision arthroplasty group. This could undoubtedly be circumstantial as we did not investigate other factors affecting this, such as antecedent antibiotic use. In addition, geographical location might play a role in differences in microbiology. A study from six countries across three continents showed varied proportions of the top ten causative

microorganisms in each country (19). We found that the most common microorganisms implicated were not different among PJI associated with internal cases *versus* referred cases. As Mayo Clinic receives referrals from throughout the United States, this subgroup of patients could be reflective of the United States as a whole. However, referred cases were mainly delayed, or late infections since acute infections are typically managed in local hospitals.

Joint age is intertwined with the microbiology of PJI. Prior reviews of data from 1969 to 2008 showed that early postoperative are more likely to be polymicrobial than late infections (20, 21). We found that early postoperative knee PJIs were more likely to be polymicrobial than late knee PJIs but did not observe the same pattern for hip PJIs. Early postoperative infections were more likely than late infections to be caused by Gram-negative and anaerobic bacteria (other than *Cutibacterium* species), as previously reported (14). Such infections are thought to be sequelae of inoculation during surgery, the initial wound healing period, or surgical site infections. Sinus tracts, which are indicators of chronicity, are also associated with these microorganisms.

Clinical implications.

Empiric antimicrobial regimens for PJI should include Gram-positive coverage as Gram-positive bacteria are the most commonly isolated organisms regardless of timing from surgery, type of arthroplasty, or geography. Vancomycin may be used in the empirical regimen. A positive culture for *Corynebacterium* species, *Enterococcus* species, Gram-negative bacteria, anaerobic bacteria (other than *Cutibacterium* species), fungi, or mycobacteria should raise the possibility of polymicrobial infection. Additional empiric Gram-negative and anaerobic antimicrobial coverage may be reasonable in such situations while awaiting final culture results. This is especially true in the presence of a sinus tract or when prior aspirate cultures have not been obtained. Withholding preoperative antimicrobials to optimize culture sensitivity and recovery of an isolate (or isolates) for susceptibility testing is crucial. Although not explored in this study, late hematogenous PJI can also be caused by Gram-negative bacteria (22). Depending on the patient's clinical status and hemodynamic stability, additional Gram-negative antimicrobial coverage might also be warranted.

A strength of our study is that our rate of culture-negative PJI was low. While other studies have reported a range of 5 to 45% for culture-negative PJI (23), we found a rate of 5%. It should be noted that there were minor differences in definitions of culture-negative PJI between studies, as this has been updated throughout the years. Studies with high rates of culture-negative PJI beget the question of the actual rates of other causative microorganisms. Modern culture techniques, such as inoculation into blood culture bottles and sonication of explanted prostheses, have increased the likelihood of finding the causative microorganism(s) (24, 25).

There are limitations to a database study as it only relies on data previously collected and not specifically for the study. Since all culture results were included, some clinically insignificant organisms (i.e., contaminants) might have been counted as contributing pathogens. Nevertheless, a smaller study from our institution in which electronic medical

records were reviewed and cross-checked found almost identical findings (26). The current study did not investigate acute hematogenous infections as the database does not capture information on bacteremia. However, acute hematogenous PJIs are more commonly caused by Gram-positive bacteremias such as *Staphylococcus aureus* complex and *Streptococcus* species than Gram-negative bacteria and other Gram-positive bacteria (27). Chronicity of infection and history of prior PJI were not part of the database, and accordingly, these variables were not assessed. The International Consensus recommends shifting away from the traditional division between acute and chronic PJI, recognizing PJI is a continuum rather than discreet disease entities (28). The microbiology of PJI is likely fluid across this continuum rather than siloed into periods. Lastly, the study was not designed to evaluate if differences in culture methods, including the number of cultures performed, impact the likelihood of culture positivity or polymicrobial infection. We believe that it did not significantly impact the distribution of microorganisms.

In conclusion, up-to-date information on microbiology is helpful to inform optimal treatment of PJI. Contemporary studies might show new patterns and expand understanding of the impact of modern surgical, medical, and diagnostic techniques on the microbiologic etiology of PJIs. Future studies should update knowledge in this area, including variables not examined here, using the most current definition of PJI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Patients with Hip and Knee PJI

	Monomicrobial n=1,448	Polymicrobial n=508	Culture-negative n=111
Age, median (IQR)	68 (60–75)	66 (59–74)	68 (61–76)
Male sex, n (%)	846 (58)	267 (53)	57 (51)
BMI, median (IQR)	32 (28–37)	33 (29–38)	35 (30–40)
ESR, median (IQR)	43 (25–67)	45 (24–75)	36 (25–43)
CRP, median (IQR)	39 (15–100)	39 (15–79)	31 (14–67)
Synovial fluid WBC/ μ L, median (IQR)	30,009 (9,472–65,036)	28,453 (3,028–70,556)	12,780 (3,625–44,561)
Sinus tract present, n (%)	184 (13)	142 (28)	20 (18)
Arthroplasty type			
Primary arthroplasty, n (%)	956 (66)	337 (66)	91 (82)
Revision arthroplasty, n (%)	492 (34)	173 (34)	20 (18)
Arthroplasty location			
Hip joint, n (%)	601 (42)	268 (53)	36 (32)
Knee joint, n (%)	847 (58)	242 (47)	75 (68)

BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

Note: Data available for 987 episodes for BMI, 1910 episodes for ESR, 1888 episodes for CRP, and 1169 episodes for synovial fluid leukocyte count.

Table 2.

Isolated Microorganisms According to Timing of Infection

Microorganism	Total N=2,067, n (%)	Early N=442, n (%)	Delayed N=305 n, (%)	Late N=1,320, n (%)	P value*
Aerobic Gram-positive bacteria	1698 (82)	372 (84)	260 (85)	1066 (81)	.8
Coagulase-negative <i>Staphylococcus</i> species (other than <i>Staphylococcus lugdunensis</i>)	761 (37)	165 (37)	115 (38)	481 (36)	.9
<i>Staphylococcus aureus</i> complex	497 (24)	140 (32)	79 (26)	278 (21)	<.001
<i>S. lugdunensis</i>	77 (4)	7 (2)	13 (4)	57 (4)	.6
<i>Streptococcus</i> species	287 (14)	36 (8)	48 (16)	203 (15)	<.001
<i>Enterococcus</i> species	155 (8)	38 (9)	20 (7)	97 (7)	.5
<i>Corynebacterium</i> species	105 (5)	32 (7)	16 (5)	57 (4)	.03
Aerobic Gram-negative bacteria	222 (11)	57 (13)	43 (14)	122 (9)	.01
Enterobacterales	143 (7)	32 (7)	28 (9)	83 (6)	.2
<i>Pseudomonas</i> species	64 (3)	16 (4)	14 (5)	34 (3)	.1
Anaerobic bacteria	262 (13)	72 (16)	35 (11)	155 (12)	.04
<i>Cutibacterium</i> species	164 (8)	45 (10)	20 (7)	99 (8)	.1
Other anaerobic bacteria	108 (5)	29 (7)	20 (7)	59 (4)	.1
Fungi	65 (3)	9 (2)	15 (5)	41 (3)	.08
Mycobacteria	12 (0.5)	3 (0.7)	6 (2)	3 (0.2)	.001

* p-value is for any difference between cells within the row.

Table 3.

Microorganisms in Monomicrobial and Polymicrobial Infections

	Monomicrobial n=1,448	Polymicrobial n=508
Aerobic Gram-positive organisms, n (%)	1207 (83)	491 (97)
Coagulase-negative staphylococci (other than <i>Staphylococcus lugdunensis</i>), n (%)	490 (34)	271 (53)
<i>Staphylococcus aureus</i> complex, n (%)	338 (23)	159 (31)
<i>S. lugdunensis</i> , n (%)	51 (4)	25 (5)
<i>Streptococcus</i> species, n (%)	180 (12)	107 (21)
<i>Enterococcus</i> species, n (%)	67 (5)	88 (17)
<i>Corynebacterium</i> species, n (%)	31 (2)	74 (15)
Aerobic Gram-negative organisms, n (%)	93 (6)	129 (25)
Enterobacterales, n (%)	61 (4)	82 (16)
<i>Pseudomonas</i> species, n (%)	28 (2)	36 (7)
Anaerobic bacteria, n (%)	113 (8)	149 (29)
<i>Cutibacterium</i> species, n (%)	87 (6)	77 (15)
Other anaerobic organisms, n (%)	28 (2)	80 (16)
Fungi, n (%)	28 (2)	37 (7)
Mycobacteria, n (%)	2 (0.1)	10 (2)

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