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Clinical Studies

Microbiology of polymicrobial prosthetic joint infection☆

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ABSTRACT

Prosthetic joint infection (PJI) is a rare but challenging complication of arthroplasty. Herein, we describe the epidemiology and microbiology of PJI, with a focus on analyzing differences between the microbiology of polymicrobial *versus* monomicrobial infection of hip, knee, and shoulder prostheses. In addition, we report the most frequent co-pathogens in polymicrobial infections, as detected by culture. A total of 373 patients diagnosed with PJI at Mayo Clinic were studied. For hip and knee arthroplasties, a higher proportion of fractures ($P = 0.02$) and a shorter time between the implantation and symptom onset ($P < 0.0001$) were noted in polymicrobial *versus* monomicrobial PJI. The most common microorganism detected, *Staphylococcus epidermidis*, was more frequently detected in polymicrobial (60%) *versus* monomicrobial (35%) PJI ($P = 0.0067$). Among polymicrobial infections, no co-pathogens were more frequently found than others, except *S. epidermidis* and *Enterococcus faecalis* which were found together in 5 cases. In addition to coagulase-negative staphylococci and enterococci, *Corynebacterium* species and *Finegoldia magna* were common in polymicrobial infections. Conversely, there was no difference between the prevalence of *Staphylococcus aureus*, Gram-negative bacilli, or *Cutibacterium acnes* between the polymicrobial and monomicrobial groups. The microbiology of polymicrobial PJI is different from that of monomicrobial PJI.

1. Introduction

Joint replacement is a common surgical procedure, improving symptoms of degenerative joint disease by relieving pain and increasing joint mobility (Osmon et al., 2013). Indeed, the prevalence of hip and knee arthroplasty is 0.8% and 1.5%, respectively, of the United States population, and the number of shoulder replacements, though smaller, has been increasing over the last 2 decades (Day et al., 2010; Maradit Kremers et al., 2015).

Although arthroplasties have high success rates, 1.5% to 2.5% are complicated by prosthetic joint infection (PJI), leading to high medical costs and complex patient care (Kurtz et al., 2012; Lentino, 2003). Because the bacteria involved grow as biofilms on both the prosthesis and in the surrounding native tissue, they can be difficult to eradicate and, as a result, often require long antibiotic therapy and additional surgeries.

In order to adapt empirical antibiotic therapy before results of cultures, an accurate understanding of the microbiology of PJI is needed. It is estimated that ~85% of PJIs involve a single bacterium. For hip and knee arthroplasties, the 2 most common microorganisms found are coagulase-negative *Staphylococcus* species (27%) and *Staphylococcus aureus* (27%), followed by Gram-negative bacilli (9%), streptococci (8%), anaerobic bacteria (4%), and enterococci (3%) (Tande and Patel, 2014). For shoulder arthroplasties, the microbiology is different, as the most frequent microorganisms are *Cutibacterium acnes,* followed by *Staphylococcus epidermidis* and *S. aureus.*

Polymicrobial PJI is conversely found in ~15% of the cases and is not well understood; for example, it is not mentioned in the Infectious Disease Society of America (IDSA) guidelines on PJI (Osmon et al., 2013). Moreover, polymicrobial PJIs appear to have a different microbiology than their monomicrobial counterparts. But there has been little research precisely describing polymicrobial PJI, mostly because of the relatively small numbers of cases and the historical limited identification of associated bacteria, a situation that has improved with the advent of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI TOF MS) (Tande and Patel, 2014). As a result, little information is available as to the frequency of the different bacteria involved in polymicrobial PJI and whether certain microorganisms have more of a predilection than others to be found in such cases.

Biofilms are structured microbial entities on surfaces consisting of clusters of bacteria surrounded by a polymeric matrix (Zimmerli et al., 2004). Although biofilms are often studied as monomicrobial rather than polymicrobial structures, they may be either. A recent trend in bacteriology is to study polymicrobial biofilm formation *in vitro* and *in vivo*. This is justified because polymicrobial biofilms are found at significant rates in infections such as those occurring in wounds (Elias and Banin, 2012; Gabrilska and Rumbaugh, 2015); however, this concept may also be applicable to PJI. Certain types of microorganisms may be more likely to grow together than separately, and there may be benefits in

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doing so (Tyner and Patel, 2016). For example, we showed that dual-species *S. aureus* and *C. acnes* biofilms enhanced survival of *S. aureus* (Tyner and Patel, 2016). This led us to hypothesize that some species may be more likely than others to form polymicrobial biofilms on prosthetic joints.

To test this hypothesis as well as to explicitly describe the microbiology of polymicrobial PJI, we conducted a retrospective epidemiologic study in which we analyzed 373 positive sonicate fluid cultures from 373 patients with infected hip, knee, or shoulder arthroplasties. We then compared the microbiology of polymicrobial *versus* monomicrobial infections for the 3 types of joint replacements.

2. Materials and methods

2.1. Study design and population

We studied 373 subjects whose specimens had been archived in the Mayo Clinic Prosthetic Joint Infection Biobank (Rochester, MN) and reviewed their clinical and microbiological findings. In total, we retrospectively reviewed 373 positive sonicate fluid cultures from patients diagnosed with PJI who underwent surgery at the Mayo Clinic between August of 2003 and March of 2017. Subjects were included provided they had a diagnosis of a PJI and significant positive sonicate culture results. If patients had more than 1 removed implant, only the first implant removal was included.

Patient characteristics recorded according to the affected joint (hip and knee, or shoulder), included age, gender, underlying joint disorder that led to the first arthroplasty, time elapsed between the first implant and infection-associated symptom onset, and whether a communicating sinus tract was present at the time of diagnosis were analyzed. The time to onset after implant surgery was defined as the number of days between the implant surgery and onset of symptoms. For patients who had chronic joint pain or limited range of motion beginning a few days after surgery, we defined the time to onset as the number of days between the implant surgery and the date of the diagnosis.

2.2. Diagnosis of PJI

Based on the IDSA guidelines, a patient was diagnosed with PJI if 1 of the following criteria was met: presence of intraoperative purulence, acute inflammation on periprosthetic tissue histopathology, sinus tract communicating with the prosthesis, or positive microbiology based on sonicate fluid culture (Osmon et al., 2013).

2.3. Sonicate fluid cultures

Prosthetic components removed from patients who had surgery for PJI were collected in a solid sterile container and subjected to vortexing/sonication culture, as previously described (Trampuz et al., 2007; Vergidis et al., 2011). We quantified and identified the sonicate fluid isolates using standard laboratory techniques, including MALDI TOF MS. For sonicate fluids collected from August 2003 to December 2005, we considered a culture significant if there was growth of greater than 5 colony-forming units (cfu)/0.5 mL of sonicate fluid (Trampuz et al., 2007). For those collected from January 2006 to March 2017, because we used a concentration step, we considered cultures significant if there was growth of greater than 20 cfu/10 mL of sonicate fluid (Cazanave et al., 2013; Piper et al., 2009).

2.4. Definitions

We considered a PJI to be monomicrobial if only 1 bacterial species had grown at a significant level from sonicate fluid cultures. In contrast, we considered a PJI polymicrobial if more than 1 species was isolated at a significant level from sonicate fluid cultures.

2.5. Ethics

Samples were collected under the Mayo Clinic Institutional Review Board protocol 09-000-808.

2.6. Statistical analysis

We described baseline characteristics of the study population as frequencies and percentages, and compared results using χ^2 tests for qualitative variables and *t* tests for continuous variables. For shoulder PJI, because the population size of the polymicrobial group was less than 5, we used a Wilcoxon test for continuous variables and a Fisher test for qualitative variables.

We summarized microorganism frequencies in both monomicrobial and polymicrobial infection as frequencies and percentages and compared results using χ^2 tests when the value was greater than 5. When fewer than 5 variables where analyzed, we used a Fisher exact text. *P* values <0.05 were considered significant.

3. Results

A total of 373 subjects with PJI met inclusion criteria and were analyzed. Because the microbiology of joint infection differs according to location, we separated PJIs by the joint type affected; 310 hip and knee arthroplasties were combined, and 63 shoulder arthroplasties were separately analyzed. We then separated them into 2 groups: polymicrobial infections and monomicrobial infections (Fig. 1).

3.1. Patient characteristics

Patient characteristics, separated by monomicrobial and polymicrobial PJI, are shown in Table 1.

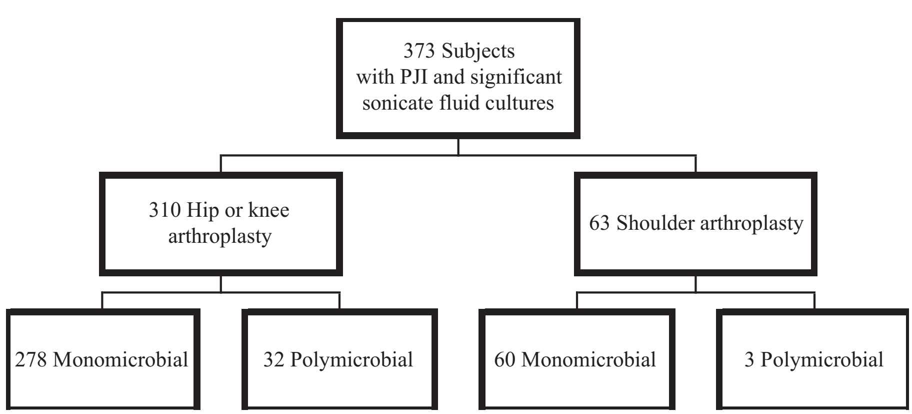

Fig. 1. Flowchart showing the distribution of monomicrobial and polymicrobial PJI cases according to hip or knee *versus* shoulder arthroplasty.

Table 1
Patient characteristics.

	Hip or knee arthroplasties			Shoulder arthroplasties		
	Monomicrobial	Polymicrobial	*P* value	Monomicrobial	Polymicrobial	*P* value
Total	**278 (90%)**	**32 (10%)**		**60 (95%)**	**3 (5%)**	
Sex: male	161 (58%)	14 (44%)	0.12	44 (73%)	3 (100%)	0.56
Age, mean in years	66 (IQR 58–75)	65 (IQR 58–71)	0.8	63 (IQR 57–65)	56 (IQR 52–70)	0.85
Underlying joint disorder						
Osteoarthritis	157 (57%)	14 (44%)	0.17	35 (58%)	2 (67%)	0.77
Fracture	30 (11%)	8 (25%)	0.02	14 (23%)	1 (33%)	0.69
Clinical presentation						
Sinus tract	78 (28%)	14 (44%)	0.065	9 (15%)	1 (33%)	0.41
Time of onset, mean ± SD in years	1452 ± 4231	193 ± 295	<0.0001	177 ± 1359	306 ± 530	0.26

IQR = interquartile range.

For hip and knee arthroplasties combined, the proportion of polymicrobial infections was 10%, and there was no difference in age, gender, osteoarthritis, or the presence of a sinus tract between the monomicrobial and polymicrobial groups. For the monomicrobial and polymicrobial hip and knee PJI groups, the median ages were 66 and 65 years, respectively. For hip and knee arthroplasties combined, the proportion of fractures was higher in the polymicrobial than in the monomicrobial group ($P = 0.02$). The time to onset of first symptoms of hip and knee PJI combined was also shorter in polymicrobial PJI, with a mean of 193 days *versus* 1452 days with monomicrobial PJI ($P < 0.0001$).

There were just 3 polymicrobial shoulder PJIs, a rate that was lower than that of hip and knees PJIs: 5%. There were no significant differences in patient characteristics between the monomicrobial and polymicrobial shoulder PJI groups; however, there were only 3 patients with polymicrobial shoulder PJI.

3.2. Microbiology

Monomicrobial hip and knee PJIs were mainly caused by *S. epidermidis* ($n = 97$, 35%) and *S. aureus* ($n = 58$, 21%), followed by *Streptococcus* species ($n = 31$, 11%), Gram-negative bacilli ($n = 21$, 8%), *Enterococcus* species ($n = 16$, 6%), non-*epidermidis* coagulase-negative *Staphylococcus* species (CoNS) ($n = 17$, 6%), *Corynebacterium* species ($n = 8$, 3%), *Granulicatella adiacens* ($n = 6$, 2%), and anaerobic Gram-positive bacteria ($n = 13$, 5%), including *C. acnes* ($n = 9$, 3%), *Finegoldia magna* ($n = 4$, 1%), and others ($n = 11$, 4%) (Table 2; Fig. 2a).

Polymicrobial hip and knee PJIs had a different distribution of species compared to their monomicrobial counterparts (Table 2). *S. epidermidis* was found in 59% of 32 polymicrobial hip and knee PJIs (Fig. 2b). The proportion of *S. epidermidis* was greater in polymicrobial than monomicrobial hip and knee PJIs ($P = 0.007$) (Table 2). *S. aureus* remained present at a rate of 22% in polymicrobial PJI with no significant difference between monomicrobial and polymicrobial hip and knee PJIs ($P = 0.9$). Non-*epidermidis* CoNS were observed at a rate of 25% in polymicrobial PJI, which was greater than in monomicrobial infections ($P = 0.0002$). In addition, enterococci were more frequent in polymicrobial than monomicrobial hip and knee PJIs, reaching a prevalence of 28% ($P < 0.0001$). *Corynebacterium* species were identified in 5 infections (16%) and were more common in polymicrobial than monomicrobial hip and knee PJIs ($P = 0.0007$). Among the anaerobic bacteria, *F. magna* was detected in 19% of polymicrobial hip and knee PJIs, which was more frequent than in monomicrobial hip and knee PJIs ($P < 0.001$). There was no difference in prevalence of *C. acnes* between monomicrobial (3%) and polymicrobial (9%) hip and knee PJIs ($P = 0.1$). Other microorganisms were detected in12% of polymicrobial hip and knee PJIs.

Table 2
Microbiology of hip and knee PJI, sorted by monomicrobial and polymicrobial cases.

Microorganism	Monomicrobial	Polymicrobial	*P* value
Staphylococcus epidermidis	97 (35%)	19 (59%)	0.007
Staphylococcus aureus	58 (21%)	7 (22%)	0.9
Other coagulase-negative *Staphylococcus* sp.	17 (6%)	8 (25%)	0.0002
Enterococcus sp.	16 (6%)	9 (28%)	<0.0001
Corynebacterium sp.	8 (3%)	5 (16%)	0.0007
Gram-negative bacilli	21 (8%)	3 (9%)	0.7
Streptococcus sp.	31 (11%)	2 (6%)	1
Granulicatella adiacens	6 (2%)	0 (0%)	-
Finegoldia magna	4 (1%)	6 (19%)	<0.0001
Cutibacterium acnes	9 (3%)	3 (9%)	0.1
Others	11 (4%)	4 (12%)	-

Lastly, there was no difference between monomicrobial and polymicrobial infections for Gram-negative bacilli ($P = 0.7$) or streptococci ($P = 1$). Among hips and knees infected by a *Streptococcus* sp., non-viridans streptococci represented 3% of the polymicrobial infections and 6% of the monomicrobial infections, while viridans streptococci represented 3% of polymicrobial and 5% of monomicrobial PJIs.

Because of the high prevalence of *S. epidermidis* in polymicrobial hip and knee PJIs, we analyzed its co-pathogens (Fig. 2c). *Enterococcus* species (5 *Enterococcus faecalis* and 1 *Enterococcus faecium*) were found with *S. epidermidis* in 6 subjects. *S. aureus, Staphylococcus haemolyticus,* and *Staphylococcus lugdunensis* were each identified twice with *S. epidermidis*. Other co-pathogens that were found once each included *Staphylococcus pseudintermedius*, *Staphylococcus saccharolyticus* plus *Corynebacterium* species, *Cutibacterium acnes*, *Cutibacterium avidum*, *Bacillus* species, and *Escherichia coli* plus *Corynebacterium aurimucosum*.

There were 25 cases of hip or knee PJI caused by enterococci, of which 9 were polymicrobial (36%). The co-pathogens were *S. epidermidis* for 6 (66%), 1 non-*epidermidis* CoNS, 1 *S. aureus,* and 1 *Dermatobacter hominis.*

In monomicrobial shoulder PJIs, the following organisms were detected: *C. acnes* (53%), *S. epidermidis* (20%), *S. aureus* (12%), *F. magna* (5%), *C. avidum* (3%), and other species (7%) (Fig. 3). The sample size for polymicrobial shoulder PJI was small ($n = 3$, 5% of infections). One polymicrobial shoulder PJI involved *C. acnes*, *S. epidermidis*, and *Corynebacterium accolens*. The other 2 were associated with *C. acnes* and *S. epidermidis*, and *C. acnes* and *Bacillus* species. Notably, *C. acnes* was found in all 3 polymicrobial shoulder PJIs, and *S. epidermidis* was present in 2 of the 3.

Seven bacteria were not identified to the species level (2 *Corynebacterium* species, 2 *Bacillus* species, 1 CoNS, and 2 viridans streptococci). The CoNS was categorized into the "co-pathogens without *S. epidermidis*" group to minimize bias in our main analysis (Fig. 2b).

4. Discussion

This study is the first to systematically report the microbiology of polymicrobial PJIs. Overall, 450 of 457 microorganisms were identified to the species level, making it possible to describe the microbiology of polymicrobial *versus* monomicrobial PJI in a relatively large sample

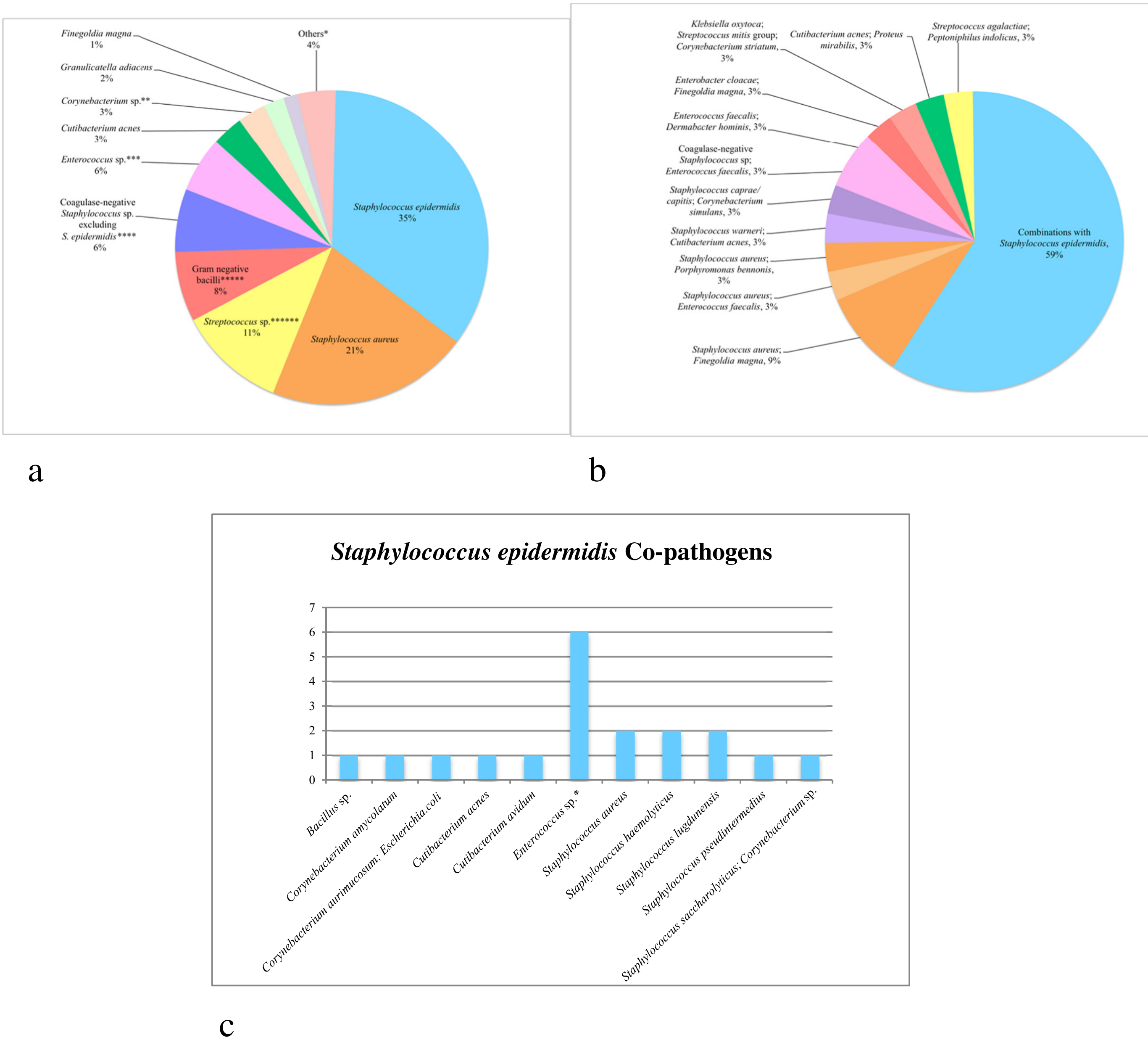

Fig. 2. a. Microbiology of monomicrobial hip and knee PJI. **LEGEND:** *1 *Aggregatibacter aphrophilus*, 1 *Capnocytophaga canimorsus*, 1 *Mycobacterium smegmatis*, 3 *Candida albicans,* 1 *Candida parapsilosis* 1 *Actinomyces naeslundii,* 1 *Actinomyces neuii,* 1 *Bacillus fragilis,* 1 *Clostridium sporogenes,* 1 *Peptoniphilus asaccharolyticus* **1 *Corynebacterium afermantans*, 1 *Corynebacterium amycolatum*, 1 *Corynebatcerium jeikeium*, 1 *Corynebacterium propinquum*, 1 *Corynebacterium pyruviciproducens*, 3 *Corynebacterium striatum*. ***12 *Enterococcus faecalis*, 3 *Enterococcus faecium*, 1 *Enterococcus gallinarum.* **** 2 *Staphylococcus capitis*, 2 *Staphylococcus caprae*, 3 *Staphylococcus caprae/capitis*, 10 *Staphylococcus lugdunensis*. *****2 *Citrobacter koseri*, 2 *Escherichia coli*, 3 *Enterobacter cloacae* complex, 1 *Proteus mirabillis*, 3 *Serratia marcescens/ureilytica*, 2 *Haemophilus influenzae*, 7 *Pseudomonas aeruginosa*. ******3 *Streptococcus anginosus*, 6 *Streptococcus mitis* group, 1 *Streptococcus mutans*, 2 *Streptococcus salivarius*, 1 *Streptococcus sanguinis*, 2 viridans group *Streptococcus* species, not further identified, 12 *Streptococcus agalactiae*, 4 *Streptococcus dysgalactiae* subspecies *equisimilis* b. Microbiology of polymicrobial hip and knee PJI. c. *Staphylococcus epidermidis* co-pathogens in hip and knee PJI. **LEGEND: *6 co-pathogens were *Enterococcus* sp.:** *Staphylococcus epidermidis* + *Enterococcus faecalis* (5 instances) *Staphylococcus epidermidis* + *Enterococcus faecium*(1 instance) *Bacillus* sp. and *Corynebacterium* sp. were not further identified.

set. We found that polymicrobial PJI tends to occur earlier following arthroplasty surgery than does monomicrobial PJI. Polymicrobial PJIs were also associated with patients who required a prosthetic joint because of a fracture. Open fractures may serve as a portal of entry for skin microorganisms. Surprisingly, there was no statistically significant difference in the percentage of subjects with sinus tracts between the 2 groups, though there was a trend towards a higher proportion in the polymicrobial group.

The population of microorganisms found in polymicrobial PJI was different than that found in monomicrobial PJI. *S. epidermidis* and other CoNS were particularly common in polymicrobial PJIs. Historically, CoNS were rarely identified to the species level in clinical laboratories because of the clinical focus on making a distinction between *S. aureus* and non-*aureus* staphylococci (Otto, 2009). Thus, many studies do not provide data on specific species of CoNS involved in PJI, including *S. epidermidis*, making it difficult to compare our results to the current literature. Still, our results are in agreement with those of a Norwegian study focused on the microbiology of PJI from 278 patients, which included 27 polymicrobial cases (10%) of which 18 (66%) were associated with CoNS (Langvatn et al., 2015). Also, a study by Figa et al. compared 14 polymicrobial to 24 monomicrobial PJIs caused by *C. acnes*, in which CoNS was found in 10 of 14 polymicrobial infections, with 3 isolates identified as *S. epidermidis* (Figa et al., 2017).

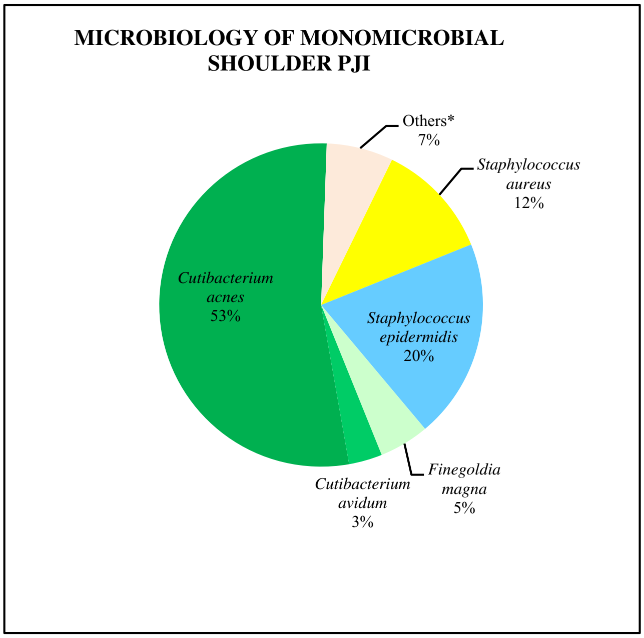

Fig. 3. Microbiology of monomicrobial shoulder PJI. **LEGEND:** *1 *Desulfivibrio* sp., 1 *Enterococcus faecalis*, 1 *Pseudomonas aeruginosa*, 1 *Streptococcus agalactiae*.

There are a several potential explanations of the prevalence of *S. epidermidis* in polymicrobial PJI. First, *S. epidermidis* is a commensal bacterium, which could be inoculated at the time of surgery, causing early-onset infection. Stewart et al. studied *S. epidermidis in vitro* in a multispecies biofilm with *S. aureus* (Stewart et al., 2017), demonstrating that *S. epidermidis* was the dominant species in the polymicrobial biofilm when given a lead time of 4 to 6 h, as well as under environmental conditions of low pH or low concentrations of vancomycin (Stewart et al., 2017). On the other hand, *S. aureus* biofilm growth was faster under unstressed conditions (37 °C; pH 7) at which it overtook *S. epidermidis* growth (Stewart et al., 2017). This could explain why *S. epidermidis*, a slow-growing bacterial species, was found in 60% of polymicrobial PJIs. Under stressful conditions, like in prosthetic joints, *S. epidermidis* may maintain stable growth, whereas more virulent bacteria, such as *S. aureus,* may not be so readily able to prosper. Importantly, relative numbers of co-pathogens in polymicrobial PJIs are not expected to be equal, making it potentially challenging to differentiate contaminants from pathogens but also meaning that some polymicrobial infections may possibly be misclassified as being monomicrobial.

Another finding in our study was the high rate of enterococci (36%) in polymicrobial PJIs. A multicenter European study focused on PJI solely caused by enterococci identified 107 cases (54%) of polymicrobial infections out of a sample of 203 patients (Tornero et al., 2014). The study also found that polymicrobial PJI occurred earlier after implantation than did monomicrobial PJI (Tornero et al., 2014). Despite the fact that our sample of enterococcal PJI was small ($n = 25$), we found comparable results, with a higher proportion of polymicrobial PJI among our *Enterococcus*-positive samples. In the prior study, enterococcal co-pathogens were CoNS in 37 cases, *S. aureus* in 24 cases, *E. coli* in 13 cases, *Pseudomonas aeruginosa* in 14 cases, *Enterobacter cloacae* in 4 cases, and other microorganisms in 15 cases (Tornero et al., 2014). Our sample of enterococcal PJI cases was too small to highlight any pattern of association with microorganisms, other than *S. epidermidis*.

Interestingly, the proportion of *S. aureus*, Gram-negative bacilli, and streptococci was not significantly different between monomicrobial and polymicrobial PJI.

There are some limitations to our study. It was a retrospective study of nonconsecutive patients, and not all hardware extracted in order to treat a PJI at the Mayo Clinic is sent for sonication. Furthermore, the findings are subject to recruitment bias since Mayo Clinic is a reference center for PJI. Most patients come to Mayo Clinic following an interval of undiagnosed infection or after treatment failure and may have undergone multiple prior surgical procedures, which could increase the rate of polymicrobial infections. We applied strict inclusion criteria to classify cultures as positive to ensure that the organisms associated with polymicrobial infections were pathogens and not contaminants. Therefore, it is possible that some polymicrobial infections may have been excluded. In addition, it is possible that some infections were mistakenly classified as monomicrobial because, when cultured, rapidly growing organisms, especially when present at a majority concentration, may have outcompeted more slowly growing organisms.

To conclude, we describe in detail the microbiology of polymicrobial PJI in our patient population. The proportion with underlying fractures was higher in polymicrobial compared with monomicrobial infections, and polymicrobial PJIs occurred closer in time to the first implant surgery than did monomicrobial infections. We found differences in the distribution of bacterial species between monomicrobial and polymicrobial PJIs, as well as between different joint types. Some microorganisms, such as *S. epidermidis*, the most prevalent organism detected overall, were found at a higher rate in polymicrobial than monomicrobial infections. The most common co-pathogen with *S. epidermidis* was *E. faecalis*. These results can be used to inform further research into polymicrobial biofilm formation, especially with *S. epidermidis*.

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