Organism Profile in Periprosthetic Joint Infection: Pathogens Differ at Two Arthroplasty Infection Referral Centers in Europe and in the United States

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Abstract

Infecting microorganism is a strong predictor of treatment success for periprosthetic joint infection (PJI). The purpose of this study was to compare the infecting pathogens causing PJI at two large infection referral centers in the United States and in Europe. In this study, 898 consecutive cases of PJI were identified at the HELIOS ENDO-Klinik Hamburg in Europe and 772 cases were identified at the Rothman Institute in the United States. The incidence of organisms at the HELIOS ENDO-Klinik Hamburg versus the Rothman Institute was: coagulase-negative *Staphylococcus* (39.3 vs. 20.2%), *S. aureus* (13.0 vs. 31.0%), *Streptococcus* (6.5 vs. 5.8%), *Enterococcus* (7.0 vs. 3.9%), anaerobic (9.0 vs. 0.9%), fungal (0.3 vs. 2.3%), mycobacterial (0 vs. 0.6%), polymicrobial (3.4 vs. 7.4%), culture negative (16.1 vs. 15.8%), and other organisms (0.9 vs. 5.4%). The percentage of methicillin-resistant *S. aureus* was significantly higher at the American center than at the European center (48.1 vs. 12.8%; $p < 0.0001$). Our findings show higher virulence and resistance organisms are more prevalent at a referral center in the United States compared with one in Europe.

Keywords
- periprosthetic joint infection
- PJI
- arthroplasty
- Europe
- United States

It is well known by the health care community that periprosthetic joint infection (PJI) is one of the most devastating complications following total joint arthroplasty (TJA). Although the overall incidence of PJI is relatively low, estimated at 0.5 to 2% following total hip arthroplasty (THA) and at 1 to 3% following total knee arthroplasty (TKA),[1–4] an immense economic burden is associated with PJI.[5–8] On the basis of a projection study, around $650 million was spent in the United States alone to treat PJI last year with the burden expected to grow rapidly over the next few years unless the trend can be reversed.[9]

Preoperative antibiotic prophylaxis and empirical antibiotic treatment are often dependent on the organism responsible for PJI.[10] Furthermore, several studies have shown that treatment outcomes for eradication of PJI vary widely depending on infecting pathogen.[11–15] For example, a study by Zmistowski et al in 2011 showed only a 52% success rate for treatment of gram-negative PJI with two-stage exchange arthroplasty.[8] In addition, methicillin-resistant *Staphylococcus aureus* (MRSA) infection is particularly difficult to treat and serves as an independent risk factor for treatment failure.[8,11] Therefore, to guide effective perioperative antibiotic prophylaxis, empirical antimicrobial therapy, and optimal surgical management, it is very important to recognize the microorganism profile responsible for PJI.[10,16,17]

Although the overall incidence of infecting organisms in PJI has remained somewhat stable over the years and across the globe, small changes in bacterial resistance patterns may have a profound impact on treatment algorithms in the future.[18–20]

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Unfortunately, the incidence of MRSA-related PJI in the United States has increased in the past several years.[6] In small part, this finding has led to adoption of two-stage exchange arthroplasty as the preferred definitive treatment for infection eradication in this country.[21] Meanwhile, one-stage direct exchange procedures are used more heavily in European versus American institutions with authors citing a reduced cost and presumed ease for the patient as justification for the use of these direct exchanges.[22]

To this point, although there have been studies comparing postsurgical treatment outcomes after PJI between the United States and Europe, there is no literature evaluating the organisms responsible for infection after TJA in these two regions. The goal of this study is to provide a direct comparison of the infecting pathogens causing PJI in both hips and knees at two high-volume tertiary infection referral centers in the United States and in Europe.

Methods

We performed a retrospective review of all intraoperative intra-articular tissue cultures taken at time of joint revision for infection from patients at two high-volume infection referral centers between 2000 and 2011. At a European orthopedic surgery center, the HELIOS ENDO-Klinik Hamburg, Germany, 898 cases of PJI (568 hips and 330 knees) were identified. At an American orthopedic surgery center, the Rothman Institute in Philadelphia, Pennsylvania, 772 cases of PJI (353 hips and 419 knees) were identified. Infected cases were identified using each institution's prospective electronic joint infection database. PJI was defined according to the clinical and laboratory parameters: (1) painful or swollen joint with or without draining sinus tract; (2) positive joint aspirate cultures; (3) elevated serum erythrocyte sedimentation rate ($>$ 30 mm/h) and C-reactive protein ($>$ 1.0 mg/dL) markers; (4) elevated white synovial white blood cell count and polymorphonuclear cell differentiation; and (5) purulence encountered intraoperatively.

Information obtained from electronic medical records included age, gender, body mass index (BMI), index joint, date of culture, culture source and medium, intraoperative culture results, duration of culture, and antibiotic sensitivity of infecting organism as tested with the standard protocol of each institution's microbiology laboratory (not all nonstaphylococcal bacteria were tested for susceptibility to every possible antibiotic). Date of index operation, operative reports from index procedure (therefore distinction between infected primary or revision), and history of preadmission antibiotic therapy were not available for all cases as both institutions serve as an infection referral center for outside hospitals. Therefore, due to the fact that $>$ 75% of infections treated were referrals, subgroup analyses for these variables were not possible.

At both institutions, patients are required to take a shower the evening before. At the Rothman Institute, patients were given a prescription for and encouraged to shower with Hibiclens wash with 4% w/v chlorhexidine gluconate (Mölnlycke Health Care US, LLC, Norcross, GA). At the HELIOS ENDO-Klinik Hamburg, shaving of incision site with clippers or razor is done in every case the day before surgery, whereas this was not routine at the Rothman Institute. No admission preoperative decolonization of nares for MRSA was undertaken routinely at each institution. In the operating room, patients' skin was prepared with isopropyl alcohol only at the HELIOS ENDO-Klinik Hamburg, whereas a variety of surgical preparation combinations including 2% chlorhexidine gluconate/70% isopropyl alcohol, 0.7% iodine povacrylex/74% isopropyl alcohol, and/or povidone iodine were used at the Rothman Institute. Perioperative antibiotics were delayed until after culture obtainment at both institutions for infected revision surgeries during the study period. During the primary arthroplasties, intravenous (IV) cefazolin was given 30 minutes before incision at the HELIOS ENDO-Klinik Hamburg, whereas IV cefazolin, clindamycin, or vancomycin was given within 60 minutes of incision at the Rothman Institute.

A minimum of three specimens were taken from each joint and sent for aerobic/anaerobic, fungal, and acid-fast bacilli culture growth. Tissues were homogenized and standard cultivation media was used to grow each type of culture. No special culture techniques such as implant sonication or PCR were used by either center. Cultures were all incubated in appropriate conditions for a minimum of 5 days. Mean duration of culture growth was 14 days at the HELIOS ENDO-Klinik Hamburg and 6.8 days at the Rothman Institute. All infections considered for the study were deep PJIs, not superficial incisional or wound infections. No data on timing of infection were available for categorization in this study; however, all possible PJIs were included from both centers, thus there was no exclusion based on timing of symptoms.

A culture was considered monomicrobial when all cultures from a given case were in agreement for both infecting organism and antibiotic susceptibility profile. A culture was considered polymicrobial when two or more unique infecting organisms were present in either a single specimen or multiple specimens from a single patient case. Culture results were then grouped according to individual species type, gram-positive versus gram-negative organism, anaerobic organisms, monomicrobial versus polymicrobial infection, and based on resistance to antibiotic sensitivity testing. All coagulase-negative staphylococcal isolates were differentiated and categorized together. Oxacillin resistance was used to classify staphylococcal organisms as resistant to methicillin.

For statistical analysis, means and frequencies were used for continuous and categorical variables, respectively. The Fisher exact test was used to compare the regional variances of the infecting organisms as well as differences between infecting organisms in the hip or knee within a particular region. Statistical significance was determined using the Bonferroni correction for multiple bivariate tests done on the same set of data. Initial statistical significance was set at $p = 0.05$ and corrected based on n number of Fisher exact tests run on data, such that the ultimate significance was $p = 0.05/n$.

Results

When comparing the 772 cases of infection at the Rothman Institute to the 898 cases of infection at the HELIOS ENDO-

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Klinik Hamburg, the mean age of patients was 66.19 and 68.14 years, respectively ($p = 0.001$). Males constituted 50.8 and 50.1% of cases at the Rothman Institute and the HELIOS ENDO-Klinik Hamburg, respectively ($p = 0.798$). The mean BMI was significantly greater in the patients treated at the Rothman Institute compared with the patients from the HELIOS ENDO-Klinik Hamburg (31.9 vs. 28.2 kg/m^2, respectively; $p < 0.0001$).

The overall incidence of infecting organism at the American and European centers is shown in ►**Fig. 1**. More than 50% of PJIs in both the United States and European centers were caused by staphylococcal organisms. The incidence of *S. aureus* infections was significantly greater in the United States center than in the European center ($p < 0.0001$, odds ratio [OR], 2.99; 95% confidence interval [CI], 2.32–3.87). Likewise, the incidence of coagulase-negative staphylococcal infections was significantly greater in the European center ($p < .0001$, OR 2.11; 95% CI 1.68–2.66). After statistical correction for multiple bivariate analyses, polymicrobial ($p = .0002$) and anaerobic ($p = .0001$) species also showed significant difference between the two centers with regards to infecting species.

As part of the "other" bacteria reported, the Rothman Institute identified infections caused by *Micrococcus*, *Bacillus*, *Corynebacterium*, *Clostridum*, and *Coryneform* species. The HELIOS ENDO-Klinik Hamburg found infections caused by *Corynebacterium* species and *Listeria monocytogenes*. The European center demonstrated a greater variety of coagulase-negative staphylococcal and *Streptococcal* species including *Staphylococcus capitis*, *Staphylococcus caprae*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, and *Streptococcus salivarius*, among others.

When analyzing the data with regard to methicillin resistance, there was a significantly greater incidence of resistant *Staphylococcal* species overall in the United States center compared with the Europe center (49.6 vs. 37.0%; $p = 0.0002$). The incidence of MRSA was significantly greater in the United States center than in the European center ($p < 0.0001$, OR, 6.27; 95% CI, 3.39–12.31) (►**Fig. 2**). The incidence of methicillin-resistant coagulase-negative *Staphylococcus* was greater in the United States cohort but this difference did not reach statistical significance ($p = 0.091$) (►**Fig. 2**). The yearly incidences of MRSA and methicillin-resistant staphylococcal infections as a percentage of all PJIs at the United States center and European center are shown in ►**Figs. 3** and **4**. Using regression analysis, there was no significant correlation with time within two centers. Further, 8/30 (26.7%) of the cases of *Enterococcus* in the United States center were vancomycin resistant, whereas 0/63 (0.0%) cases of *Enterococcus* at the European center were resistant.

After breaking down the cases of infection by joint type, only culture negative infections within the European center showed a significant difference between knees and hips (25.2 vs. 10.9%, respectively; $p < 0.0001$). There were no other significant differences in infecting organisms when comparing knees to hips within either institution (►**Table 1**).

Discussion

Deep joint infection after TJA was characterized by Charnley and Eftekhar in their 1969 study where they account that greater than 50% of their infections were due to *S. aureus* (no methicillin resistance reported in any cases), 20% were culture negative, and the rest were due to *Bacillus proteus*, *Staphylococcus albus*, and *Streptococcus agalactiae*.[23] Many studies since then have described the bacterial incidence in isolated series of PJIs; however, there have been no studies comparing the infecting organisms between international groups. This study addressed the potential differences in organism profile in PJI of both THA and TKA between two infection referral centers in the United States and Europe.

The current study, which examined cultures from two regions between 2000 and 2011, concurred with organism profiles from previous studies done in either the United States or Europe. The studies from the United States by Fitzgerald, Fulkerson et al, and Schinsky et al show that an increasing percentage of PJIs in American centers are due to *S. aureus* (►**Table 2**).[18,19,24] Meanwhile, studies from long-term

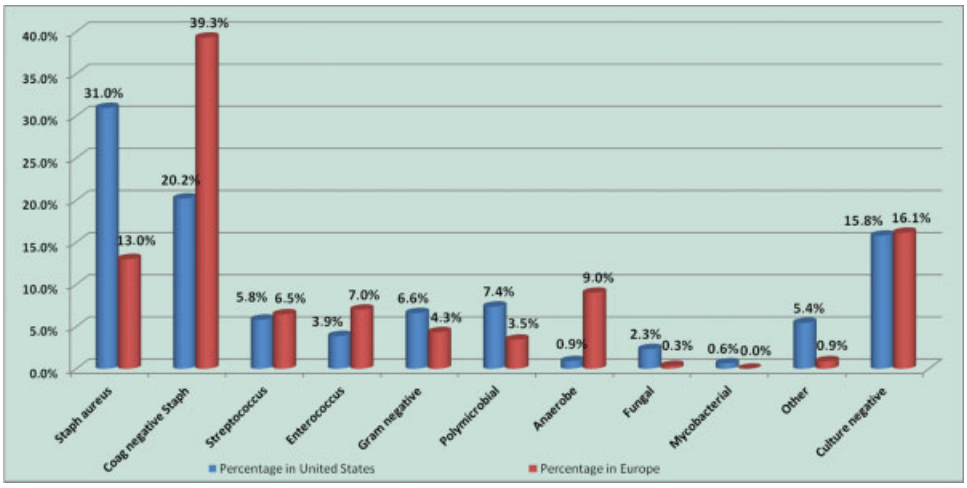

Fig. 1 Organism profile difference in incidence between the Rothman Institute (United States) and Endo-Klinik (Europe).

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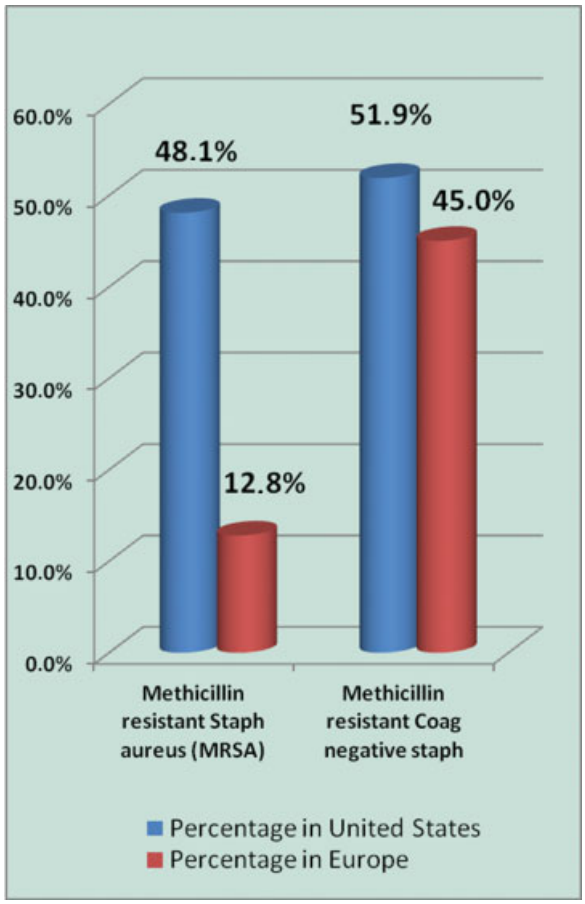

Fig. 2 Methicillin resistance profiles of staphylococcal species in Europe and United States.

prospective European registries including Stefánsdóttir et al in Sweden and Phillips et al in the United Kingdom show a greater contribution of coagulase-negative *Staphylococcus* and *Streptococcus* species when compared with *S. aureus* (►**Table 2**).[3,25] Both the current study and those studies previously mentioned show that, on average, a greater proportion of PJIs in European centers may be due to lower virulence organisms such as coagulase-negative staphylococcal and *Streptococcus* species (non–group A *S. pyogenes* species) compared with PJIs reported in American centers.

Importantly, our study demonstrates an increased proportion of methicillin-resistant organisms responsible for PJI at the American center compared with the European center. We found 48.1% of *S. aureus* infections to be due to MRSA at the Rothman Institute, whereas just 12.8% of *S. aureus* was due to MRSA at the HELIOS ENDO-Klinik Hamburg. Only one study about PJI by Phillips et al from a specialist orthopedic hospital in the United Kingdom reports on antibiotic susceptibility of *S. aureus* species for literature comparison: the authors account that only 13.6% of *S. aureus* infections were due to MRSA.[3] The higher prevalence of antimicrobial-resistant organisms in the United States has been reported previously through the MRSA nasal carriage rates in healthy adult populations, exceeding 1.5%, and increasing from 2000 to 2005.[26,27] The European Center for Disease Prevention and Control reports substantial variability in methicillin resistance of staphylococcal species between countries in the continent. However, the overall prevalence of resistance is still lower than in the United States, with Scandinavian nations such as Sweden and the Netherlands showing extremely low resistance and MRSA nasal colonization rates of 0 and 0.11%, respectively.[28–30]

There may be several potential reasons for the difference in methicillin resistance characteristics seen in the two institutions in our study, including host factors and hospital infection control practices. Although we lacked sufficient data to compare comorbidity indices between patients at the two institutions in our study, we found a significant difference in BMI (31.9 vs. 28.2 kg/m^2; $p < 0.0001$). Several reports have questioned whether increased obesity may in fact lead to higher rates of antimicrobial resistance, specifically due to inadequate antibiotic dosing in these larger patients.[31,32] Further studies will be needed to definitively correlate dosing of antibiotics in obese patients with the resulting antibiotic resistance of infecting organisms in PJI. However, an initial

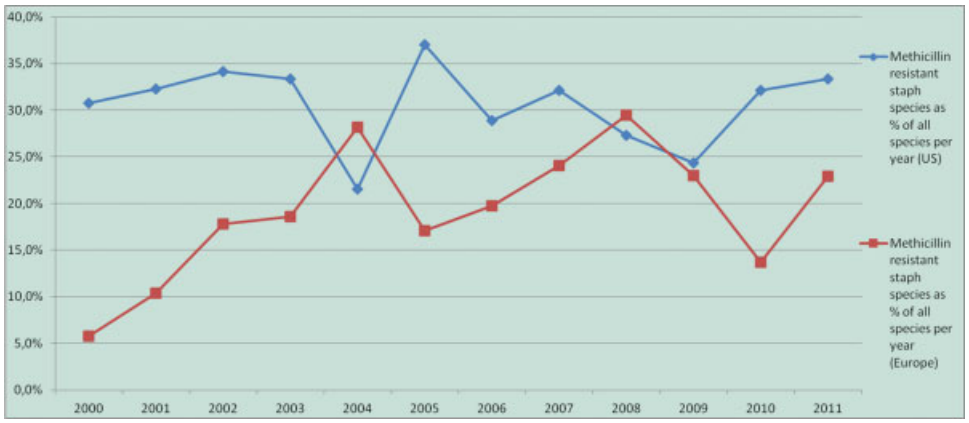

Fig. 3 Yearly trends of methicillin resistance staphylococcal species (as percentage of total PJIs in given year) between U.S. center and European center.

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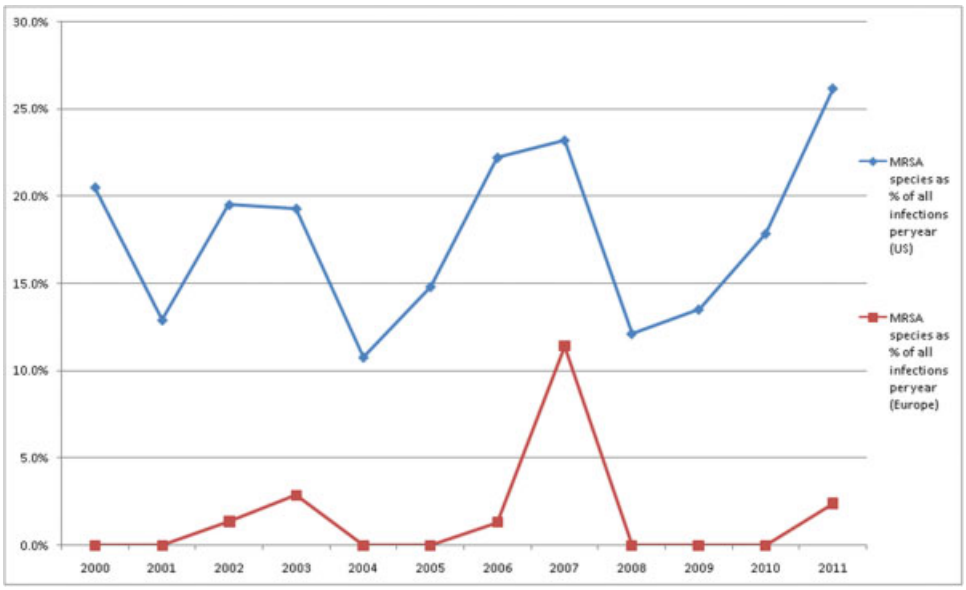

Fig. 4 Yearly trends of MRSA species (as percentage of total PJIs in given year) between United States and Europe.

step may be to determine what percentage of obese patients undergoing TJA are not receiving therapeutic doses of perioperative antibiotics during primary and revision surgery.[32,33] With regard to infection control policies, the HELIOS ENDO-Klinik Hamburg in our study restricts use of vancomycin to only those cases with proven MRSA infection or colonization, while the use of vancomycin at the Rothman Institute may have been a bit more liberal, including patients with penicillin allergies. Furthermore, the HELIOS ENDO-Klinik Hamburg bans use of scrubs outside of the operating room and disallows footwear worn in the operating room to be worn outside of the operating room —practices which were not routine at the Rothman Institute. Northern European nations such as the Netherlands, which have some of the world's lowest emergence of resistant organisms, also attribute their resistance rates to comprehensive infection control policy and restrictive use of antibiotics.[28] With regard to the study design and methodology, only the difference in anaerobic species may be potentially attributable to the significant difference in mean culture incubation time, as the longer the incubation, the higher the percentage of indolent anaerobe grown.

The difference in organism profile between reconstruction centers in Europe and in the United States has significant implications regarding patient treatment methods and infection eradication. With the emergence of highly virulent and resistant strains of bacterial pathogens, surgeons in the United States have been forced to use high potency antibiotics such as vancomycin in an increasing number of patients.[10,14,34] This may lead to development of even more difficult to treat PJI given the limited availability of antibiotics used to eradicate new organisms such as vancomycin-

Table 1 Knee and hip data for the United States center and European center

	United States		Europe	
Type of organism	Knees (%)	Hips (%)	Knees (%)	Hips (%)
Staphylococcus aureus	29.6	32.6	12.1	13.6
Coagulase-negative *Staphylococcus*	21.7	18.4	37.0	40.7
Streptococcus and *Enterococcus*	10.3	9.1	14.5	12.9
Gram negative	6.4	6.8	4.5	4.2
Polymicrobial	7.4	7.4	3.3	3.5
Anaerobe	0.5	1.4	2.4	12.9
Fungal	2.9	1.7	0.3	0.4
Mycobacterial	0.5	0.8	0.0	0.0
Other	4.5	6.5	0.6	1.1
Culture negative	16.2	15.3	25.2	10.9

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Table 2 Organism profiles for PJI reported in current study and selected existing literature

	Number of cases analyzed	*Staphylococcus aureus* (%)	Coagulase-negative *Staphylococcus* (%)	*Streptococcus* (%)
Data from the United States				
Current study	772	31.0	20.2	9.7
Fitzgerald 1995	105	18.1	28.6	18.1
Fulkerson et al 2006	146	35.0	31.0	11.0
Schinsky et al 2008	55	43.6	20.0	10.9
Data from Europe				
Current study	898	13.0	39.3	13.5
Stefánsdóttir et al 2009	426	33.6	31.0	18.4
Phillips et al 2006	74	25.0	36.0	16.0

Abbreviation: PJI, periprosthetic joint infection.

resistant enterococcus.[35] With regard to differences in surgical management, studies in both geographic regions have agreed that two-stage exchange arthroplasty is a successful procedure with eradication rates ranging from 82 to 100%.[21,36,37] European literature, however, also promotes the conservative single procedure approach for infection eradication: Romano et al cite an 81.9% success rate at an average 40.7 months follow-up,[38] whereas Klouche et al even report a 100% success rate in 38 patients at minimum 2 years follow-up. In the United States on the other hand, there remains a significant hesitancy to perform one-stage direct exchange procedures, especially in situations where the infecting organism is *S. aureus*.[39] Given the results of our study, future studies may need to examine the link between the greater number of *S. aureus* and antibiotic resistant PJIs in the United States and the caution of poor outcomes with direct prosthesis exchange in this region.

Our study is inherently limited by its retrospective design, which interferes with a consistent method of obtaining and analyzing cultures at each of the institutions. However, at both centers included in the study, standard institutional protocols for PJI were followed including obtaining at minimum three tissue cultures during surgery and growing specimens on standard media for at least 5 days. Second, since both institutions included are tertiary infection referral centers, there are several preoperative variables that we were unable to assess for their effect on specific type of infecting organism including date of index procedure, revision versus primary arthroplasty, and history of preoperative antibiotic therapy administration. Nonetheless, because the centers are huge referral centers for infection, we had the advantage of reporting on an enormous number of PJI cases with regard to infecting pathogen, more so than any study we are aware of in the current literature. Each cohort was an accurate representation of the predominant patient populations undergoing TJA in their respective geographic location, including the differences in patient demographics. Finally, it is important to note that although the two institutions included are well representative of the patient populations in the geographical regions, the results from this study must be examined with care and may not precisely represent all possible centers in the United States or in Europe.

Conclusion

Findings from our study show that the infecting organisms in PJI differ between an orthopedic center in Europe and in the United States. Not only are higher virulence organisms more prevalent in the American institution but a significantly greater resistance profile was discovered in the United States as well. Further studies will be needed to determine if the bacterial profile responsible for PJI in the two regions may be related to the difference in preferred surgical algorithms and reported outcomes after treatment. In general, the organism profile of each location will continue to play a large role in infection prevention and therapy after TJA.

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