Hip and Knee Section, Pathogen Factors

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Hip and Knee Section, Pathogen Factors: Proceedings of International Consensus on Orthopedic Infections

Julia Herkenhoff Carijo, Paul M. Courtney, Karan Goswami, Hannah Groff, Daniel Kendoff, Juliana Matos, Nemandra A. Sandiford, Henk Scheper, Carolina Arana Stanis Schmaltz, Igor Shubnyakov, Timothy L. Tan, Marjan Wouthuyzen-Bakker

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hip and knee organism profile
geographic variance in organism profile
streptococcal periprosthetic joint infection (PJI)
culture negative staphylococcal enterococcal Pseudomonas methicillin-resistant Staphylococcus aureus (MRSA)

Question 1: Does the virulence (low or high) of the infecting organism affect the treatment of acute hematogenous or chronic periprosthetic joint infections (PJIs)?

Recommendation:

There is currently no evidence showing that the virulence of an infecting organism affects the treatment of acute hematogenous or chronic PJIs.

Level of Evidence: Limited
Delegate Vote: Agree: 69%, Disagree: 27%, Abstain: 4% (Super Majority, Weak Consensus)

Rationale:

Pathogenicity is the ability of an agent to cause disease. The degree to which a pathogenic microorganism can cause an infectious disease is determined by its virulence. Several factors determine the virulence of bacteria, such as the bacterial capsule, presence of adhesin proteins, degradative enzymes, toxins, and mechanisms for escaping elimination by host defenses (e.g., intracellular invasion and survival or production of biofilm). In addition, the host susceptibility to an infection also depends on its immune status and the presence of the foreign material [1]. The type of virulence factor(s) expressed participates in the clinical presentation of disease. In general, microorganisms that are considered highly virulent tend to cause acute infections (e.g., Staphylococcus aureus, streptococci or gram-negative bacilli) [2]. In contrast, pathogens with lower virulence are associated with chronic infections (e.g., Cutibacterium acnes, Staphylococcus epidermidis, and other coagulase-negative staphylococci [CoNS]) [2]. However, whether all virulence factors of a bacterium become expressed and to which degree greatly depends on the presence of specific environmental stimuli [3]. For this reason, we will address this question in two ways: (1) we evaluated the difference in virulence among different microorganisms (e.g., classically highly virulent microorganisms vs low-virulence microorganisms) affects treatment outcomes and (2) we evaluated whether the degree of virulence factors expressed within one species affects treatment outcomes.

Degree of Virulence Among Different Microorganisms and Its Relation to Outcomes

A PubMed search was performed for the late acute/hematogenous periprosthetic joint infections (PJIs) and chronic PJIs in relation to the treatment outcome. All relevant articles were screened
The total number of patients was counted in both groups, and a treatment success rate was found to be 90% (range 87%-100%) with a debridement, antibiotics, and implant retention (DAIR) procedure was 56% (range 35%-94%). For chronic PJIs, 1 meta-analysis (including 62 studies) and 6 published studies thereafter were included [19–25]. Of 4570 patients with chronic PJIs, the treatment success rate was found to be 90% (range 87%-100%) with 1-stage or 2-stage exchange procedures. The outcome of acute and chronic infections is influenced by many factors, with the greatest difference being the surgical strategy used for acute versus chronic PJI—exchange versus no exchange of the prosthesis, respectively. Owing to the heterogeneity in treatment methods, it is not possible to conclude whether the worse outcomes observed in acute infections are due to the virulence of the bacteria. There are few studies that evaluate high- versus low-virulence microorganisms using the same surgical approach. Fink et al. [27] studied 39 patients with the early PJs and 28 patients with acute hematogenous infections all of whom were treated with DAIR and followed up for a minimum of 2 years to investigate the success rate in infection eradication. There was no difference in outcomes between infection caused by higher virulence pathogens (S aureus, streptococci, enterococci, gram-negative bacilli) when compared with lesser virulence pathogens (CoNS and anaerobes such as C. acnes) [27].

Other authors have also compared the outcomes between S aureus and CoNS PJIs. One study retrospectively examined chronic PJIs treated with suppressive antibiotic therapy [28], while another investigated the outcome of S aureus PJIs versus CoNS PJIs treated with one or two stage revision [29]. Acute hematogenous and early PJI treated with DAIR and chronic knee PJI treated with different surgical modalities has also been examined in the literature. None of these studies found a significant difference in the success rate after a minimum follow-up of 3 to 24 months [4,5,13–16]. Some authors have even described a worse outcome in patients with PJI caused by CoNS [4]. These findings suggest that virulence is not a risk factor for worse outcomes in PJI.

There are some observational studies that propose that Staphylococcus species are associated with recurrence or persistence of infection, because of the high capacity to form biofilms observed within this genus [30–32]. Others have suggested that S aureus in particular is associated with a worse outcome than other microorganisms in general after DAIR [5,6,33,34] and after 2-stage revision [35]. However, other studies do not observe any significant differences in outcomes of staphylococcal infections in general [36–38].

### Degree of Virulence within the Same Species and Its Relation to Outcome

Environmental stimuli play a large role in the phenotypic expression of virulence factors [3]. For example, it has been demonstrated that the amount of magnesium present in the environment of S aureus determines the down or upregulation of specific virulence genes [15]. The resulting phenotypes have been shown to be associated with different infection outcomes in a murine model [15]. In addition, there is much debate over which virulence determinants of S aureus are primarily responsible for infection severity in osteomyelitis [4,14,16]. Although some studies identified virulence determinants or bacterial strains involved in bone and joint infections [6,13,16,17], few evaluated whether the presence or absence of these virulence factors in PJI determines treatment outcomes [6,17,18].

The literature search revealed 3 studies that examined the virulence within one species in relation to clinical outcomes [4,15,16]. Tande et al. [28] evaluated the outcome of PJs caused by staphylococcal small colony variants (SCVs), a phenotype that has been associated with intracellular persistence and biofilm formation. Despite the general hypothesis that this phenotype is primarily responsible for infection severity in osteomyelitis [4,14,16], several studies identified virulence determinants or bacterial strains involved in bone and joint infections [6,13,16,17], few evaluated whether the presence or absence of these virulence factors in PJI determines treatment outcomes [6,17,18]. Other authors have also compared the outcomes between S aureus and CoNS PJIs. One study retrospectively examined chronic PJIs treated with suppressive antibiotic therapy [28], while another investigated the outcome of S aureus PJIs versus CoNS PJIs treated with one or two stage revision [29]. Acute hematogenous and early PJI treated with DAIR and chronic knee PJI treated with different surgical modalities has also been examined in the literature. None of these studies found a significant difference in the success rate after a minimum follow-up of 3 to 24 months [4,5,13–16]. Some authors have even described a worse outcome in patients with PJI caused by CoNS [4]. These findings suggest that virulence is not a risk factor for worse outcomes in PJI.

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Recommendation:
Polymicrobial periprosthetic joint infections (PJIs) demonstrate inferior treatment outcomes when compared with monomicrobial PJIs. This finding is true for both patients treated with irrigation and debridement and 2-stage exchange arthroplasty.

Level of Evidence: Moderate
Delegate Vote: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

Rationale:
Polymicrobial periprosthetic joint infections (PJIs) are not uncommon with a reported rate between 6 and 37% [41–44]. Although common organisms such as Staphylococcus aureus are commonly isolated in these infections, more virulent organisms such as Enterococcus species, gram-negative bacilli, methicillin-resistant Staphylococcus aureus, and anaerobic bacteria are more commonly associated with polymicrobial rather than monomicrobial infections [45]. Despite the relative frequency of polymicrobial PJIs, there is minimal literature regarding treatment outcomes of polymicrobial PJIs and how they compare with monomicrobial PJIs.

The literature demonstrates that polymicrobial PJIs have inferior outcomes when compared with monomicrobial PJIs. Tan et al [46] demonstrated that patients with polymicrobial PJIs had a higher failure rate (50.5%) compared with monomicrobial (31.5%) and a higher rate of amputation (odds ratio [OR] 3.80, 95% confidence interval [CI]: 1.34–10.80), arthrodesis (OR 11.06, 95% CI: 1.27–96.00), and mortality (OR 7.88, 95% CI: 1.60–38.67) compared with patients with monomicrobial PJIs. Similarly, Wimmer et al [47] demonstrated that the infection-free rate after 2 years was 67.6% for polymicrobial infections versus 87.5% for monomicrobial infections in a series of 77 polymicrobial PJIs. Furthermore, Marculescu et al demonstrated that the 2-year cumulative probability of success of polymicrobial PJIs was 63.8% (95% CI, 43.8–80.5%) and of monomicrobial PJIs was 72.8% (95% CI, 63–80.9%). However, this difference was not significant.

The outcomes appear to be poor for polymicrobial PJIs, regardless of surgical treatment. Tan et al [46] demonstrated that the infection-free survival for polymicrobial PJIs was 55.4%, 49.3%, and 49.3% for the 2-stage exchanges and 43.2, 43.2, and 38.4% for irrigation and debridement (I and D) at 2, 5, and 10 years. Although this result was not statistically significant, there was a trend toward higher treatment success (P = .164) for 2-stage exchange arthroplasty. In Marculescu et al [45], the 2-year survival free of treatment failure for polymicrobial PJIs was 77.7% and 52.7% compared with 83.9 and 54% for monomicrobial PJIs, for 2-stage exchange arthroplasty and I and D, respectively. This rate was higher but not statistically significantly different from the polymicrobial PJIs treated with similar surgical modalities (P = .24 and P = .64). Bozhkova et al [48] also revealed that treatment success after the first stage of the 2-stage procedure was considerably higher (74.8%, n = 101) in patients with monomicrobial infection, compared with only 27.8% (n = 15) in the polymicrobial group (P < .0001). Furthermore, they found that gram-negative PJIs in polymicrobial PJIs were associated with failure as the proportion of polymicrobial PJIs caused by gram-negative pathogens was 61.5% in patients with recurrent infection and only 26.7% in patients with treatment success (P = .03). According to the data of Torner et al [49], for I and D and retention of the prosthesis, polymicrobial infection was significantly associated with failure in the global cohort (59.3% vs 40.7%, P = .036). Only one study did not show the difference between the outcome of polymicrobial and monomicrobial PJIs [50]. However, this can be explained by the insufficient number of PJI cases (only 15 cases) and pathogen properties (C acnes in isolation or together with coagulase-negative staphylococci).

There are several explanations for the increased rate of failure in patients with polymicrobial PJIs. One factor is that drainage, and the presence of a soft tissue defect have been found to be associated with polymicrobial PJIs [45,46]. Another is that polymicrobial PJIs are associated with organisms that are difficult to treat such as Enterococcus and gram negatives [44–46] that have been associated with worse outcomes [51,52]. In addition, several studies have demonstrated that patients with polymicrobial PJIs have increased comorbidities and are older than patients with monomicrobial PJIs [45,46], which likely affects their ability to eradicate an infection.

Question 3: Is there a difference in the type of pathogens that can cause SSIs/PJIs between hip and knee arthroplasty?
Recommendation:
There is limited evidence to support a difference in the organism profile causing surgical site infections (SSIs) and periprosthetic joint infections (PJs) between hip and knee arthroplasty. Isolated studies have reported an increased prevalence of streptococcal and culture-negative PJIs around the knee, whereas staphylococcal, enterococcal, and pseudomonal PJIs may be more prevalent around the hip. Further work regarding the different flora in these respective body regions is needed as it may determine antibiotic selection.

Level of Evidence: Limited
Delegate Vote: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

Rationale:
Several studies have investigated the profile of organisms causing surgical site infection (SSI) and periprosthetic joint infection (PJI) after orthopedic procedures with varying results. Staphylococci species are the most commonly isolated agents in orthopedic prosthetic infections. According to recent literature, these pathogens are the primary source of up to 72% of infections [42,43,53,54]. Bacterial resistance has become a significant problem with certain studies reporting that up to 27% of PJIs are caused by methicillin-resistant organisms [55,56]. The prevalence of resistance also appears to be rising [57].

The published literature depicts Staphylococcus aureus (S aureus) as the leading cause of PJIs after total joint arthroplasty [41,53,58]. A 14-year study evaluating the microbiological profile of PJIs after 2-stage revision from 1998–2011 found increased infection rates of methicillin-resistant S aureus (MRSA), C acnes, and Streptococcus viridans (S viridans) with no change in gram-negative, gram-positive, or fungal infections [59]. Another study investigating 121 patients diagnosed with PJIs after total knee arthroplasty (TKA) identified an increase in the prevalence of coagulase-negative Staphylococcus (CoNS) between 1994 and 2004, while S aureus appeared to decrease [60]. A separate study conducted by Uçkay et al [61] evaluated resistance in CoNS orthopedic infection over a 13-year period and did not identify any change in methicillin resistance rates associated with CoNS.

Aggarwal et al [58] identified 2 different organism profiles when comparing 772 cases of PJIs from the Rothman Institute in the United States (US) to 898 cases at HELIOS ENDO-Klinik Hamburg in Europe. The center in Europe had fewer S aureus infections (13.0% vs 31.0%) but more CoNS PJIs than the US site (39.3% vs 20.2%). There was also a significantly higher incidence of MRSA at the US center (48.1% vs 12.8%; P < .0001). However, there appears to be conflicting evidence regarding increasing prevalence of resistance in PJIs [57].

The incidence of PJIs affecting TKA versus total hip arthroplasty (THA) has been estimated at 1% to 3% and 0.3 to 2%, respectively [41,58,59]. Several studies have examined the organism profile causing PJIs after arthroplasty, but few have identified any significant difference in the profile between hip and knee arthroplasty.

Pulido et al [41] noted a higher rate of PJIs in patients undergoing TKA (1.1%; 48 of 4185) compared with THA (0.3%; 15 of 5060;
A 14-year study identified a linear increase in MRSA, *S. viridans*, and *C. acnes* causing PJIs after arthroplasty from 1998 to 2011. However, they identified no difference among organisms causing PJIs in TKA and THA (*P > .05*) [59]. *Enterococcus* was found in the majority of THA (68%) but was not considered significant after a Bonferroni correction was performed comparing THA and TKA [59].

In a large multi-institutional study evaluating the organism profile causing PJIs at two different academic centers, it was found that knees had more culture-negative infections at one of the 2 centers compared with hips. However, there were no other significant differences in the organism profile when comparing hips and knees [58]. Drago et al evaluated the organism profile and antibiotic susceptibilities of 429 patients diagnosed with PJIs from 2013 to 2015 including 229 knee and 200 hip infections. Again, the authors found no difference in the pathogen profile between hips and knees. *Staphylococci* were still the predominant organism affecting hips and knees followed by *Enterobacteriaceae* and *C. acnes*. However, methicillin resistance in CoNS was twice as prevalent around the knee versus the hip. Increased resistance to glycopeptides and fluoroquinolones was also observed around the knee in comparison to the hip [62]. Future studies should aim to further investigate these potential differences in the organism and resistance profiles in hips and knees diagnosed with SSIs and PJIs.

Groff et al recently examined 1214 PJI cases (501 hips and 713 knees) over a 17-year timeframe and found significant differences in pathogens causing PJIs in the hip and the knee. A higher incidence of streptococcal species (odds ratio [OR] 1.82, 95% confidence interval [CI] 1.23-2.67) and culture-negative PJIs (OR 1.53, 95% CI 1.12-2.09) were identified in TKA compared with THA. In contrast, *Pseudomonas* (OR 2.123, 95% CI 1.04-4.34), *Enterococcus* (OR 1.72, 95% CI 1.03-2.86), resistant species (OR 1.64, 95% CI 1.19-2.25), *S. aureus* (OR 1.40, 95% CI 1.11-1.77), and gram-positive (OR 1.37, 95% CI 1.05-1.78) organisms were more prevalent in hips. The authors suggested that the higher rates of urogenital associated pathogens causing PJIs in hips may have been related to the close proximity of the incision to the flexural creases and the groin region.

Although most studies have not demonstrated a definitive difference in the organism profile between hips and knees, some have identified differences in virulence patterns, culture-negative rates, urogenital and fecal bacteria, and the overall rates of PJIs in bilateral compared with unilateral TKA [41,58,59,62]. It is important to further delineate the differences in the organism profile at these anatomic sites to establish adequate protocols and select antimicrobials accordingly that may account for potential differences in the pathogenic flora and mitigate the risk of SSI/PJI.

**Question 4: Is there a difference in the organism profile that causes periprosthetic joint infections (PJIs) in different countries?**

**Recommendation:**

Yes, there is a difference in the organism profile causing periprosthetic joint infections (PJIs) in different countries and regions of the world. There seems to be a higher incidence of PJIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States and Australia compared with Europe.

**Level of Evidence:** Moderate

**Delegate Vote: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)**

**Rationale:**

General strategies to prevent the occurrence of periprosthetic joint infections (PJIs) have become more relevant over the last few years. As one recommendation of the International Consensus Meeting on Periprosthetic Joint Infection in 2013, surgical antibiotic prophylaxis with either single or 24-hour dose of cephalosporin should be performed. However, antibiotics (prophylactic and therapeutic) should be selected to cover the most frequently encountered pathogens, which might vary regionally, nationally, and internationally (and could be affected as well by other factors) and not simply be administered empirically.

To date, several authors have described the bacterial incidence in isolated series of PJIs with either single-center or multicenter studies. However, the comparison of organism profiles causing PJIs among countries or world regions has been evaluated by relatively few studies.

A study comparing organism profiles between PJI referral centers in the United States (US, Rothman Institute) and Europe (ENDO-Klinik) found that the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) pathogens was significantly higher in the US than in Europe [62]. In addition, a higher incidence of more virulent organisms was found in the US patient cohort in this study. Stefnodottir et al and Phillips et al in their study also found a higher incidence of coagulase-negative *Staphylococcus* and *Streptococcus* pathogens compared with *Staphylococcus aureus* within various European registries (United Kingdom [UK] and Sweden) [57,63].

Peel et al [44] showed that causative pathogens in PJIs differ significantly in Australia compared with other reported studies and geographic regions such as the US, Sweden, and the UK. In particular, the rates of polymicrobial infections showed high differences (36% vs 14%), as did the isolation of MRSA (over 40% of all cases), as compared with previous European and the US reports. Pakroo et al [64] reported similar geographic variation in organisms causing spinal infections in patients presenting to a tertiary referral center in the UK. The epidemiology and antibiotic susceptibility of bacteria causing skin and soft tissue infections do show geographic variation (e.g., between the US, Germany, Italy, and Spain) differentiating between MRSA, methicillin-sensitive *Staphylococcus aureus*, and coagulase-negative *Staphylococcus* pathogens [65]. Although these data that relate predominantly to general skin infections cannot be easily transferred to PJIs, it has been well accepted that such local infections (at the time of surgery or after) subsequently might lead to PJIs.

Furthermore, it has been shown that community-acquired soft tissue MRSA infections have a much higher incidence in the US compared with Europe [66]. While a large percentage of soft tissue infections are caused by community-acquired MRSA in the US, the community-acquired MRSA cutaneous infection rate in Europe only accounts for between 1 and 3% of presenting wound infections [67].

Along with this geographic variability, Anthony et al [68] found a seasonal variability of surgical site infections in total knee arthroplasty and THA, with seasonal increase of SSIs between 30 and 19% in patients with total knee arthroplasty or THA procedures, respectively, in the summer months, suggesting the possibility that geographic temperature conditions might influence the incidence and etiology of PJIs. These data were extracted from a US national database.

Data from several multicenter, retrospective studies have demonstrated that the organisms causing PJIs vary by the country or region of the world. An increasing number of PJIs are being caused by more virulent and resistant organisms such as MRSA in the US and Australia. With the literature lacking large prospective studies, we assign a moderate recommendation.

**References**


