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General Assembly, Diagnosis, Pathogen Isolation: Proceedings of International Consensus on Orthopedic Infections

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Question 1: Is there a method to detect sessile microorganisms that have resulted in an infection following orthopedic procedures?

Recommendation:

Yes. Molecular techniques such as polymerase chain reaction (PCR), next-generation sequencing (NGS), and synovial biomarkers such as alpha-defensin or leukocyte esterase have been shown to be powerful tools in detecting prosthetic joint infections (PJIs) with negative cultures, although conflicting data exist on PCR. Sonication of explanted prosthetics can enhance both the sensitivity of conventional cultures and PCR.

Level of Evidence: Strong

Delegate Vote: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

Rationale:

The colonization of prostheses by sessile bacteria is a feared complication of orthopedic procedures. These microorganisms anchor themselves to the surface of prosthetic implants and form a colony of immobile bacteria cross-linked by an extracellular matrix of polymeric substances, known as biofilm [1]. The presence of biofilm on prosthetic implants, especially that of prosthetic joints, makes both detection and treatment of infections difficult [2]. Although there is no "gold standard" for definitive diagnosis of prosthetic joint infections (PJIs), a multi-criteria definition created by Musculoskeletal Infection Society (MSIS) is often used to diagnose PJIs [3,4]. The MSIS criteria use the obtaining of cultures of joint aspirate or periprosthetic tissue as one of the major criteria to prove the presence of pathogens in the prosthetic joint. Unfortunately, cultures can be unreliable when detecting biofilms [5,6]. Intraoperative cultures alone also can have a high rate of contamination and false positives [7]. Thus, alternative methods for confirming the presence of organisms in PJI have been proposed [8,9]. Some of these diagnostic techniques include polymerase chain reaction (PCR), next-generation sequencing (NGS), prosthesis sonication, and joint biomarkers.

Polymerase Chain Reaction

The use of PCRs to detect bacterial nucleic acids in prosthesis infections can be an effective way of detecting sessile microorganisms otherwise not picked up in cultures [10,11]. PCR sequencing of bacterial ribosomal nucleic acids has shown to have higher sensitivity in detecting bacteria than cultures, as well as identifying polymicrobial infections that may not be picked up by cultures [12–15]. Jahoda et al showed that the use of PCR can detect as few as 590 CFU of *Staphylococcus aureus*, making detection of PJIs even in the presence of antibiotics feasible [11]. PCR has also shown

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benefit in detecting genes responsible for biofilm production and methicillin resistance [11,16].

In spite of the literature describing the merits of PCR, there are data suggesting that the efficacy of PCR is not as high as once thought. Studies have suggested that PCR has similar or less sensitivity for detecting bacteria in PJIs as traditional cultures [17–20]. PCR has also been shown to have questionable sensitivity over the last few years. A meta-analysis performed by Jun et al looking at online databases from 2013 to 2017 showed that there has been a decrease in pooled sensitivity compared with a previous meta-analysis performed by Qu et al in 2013 (0.76, 95% confidence interval [CI] 0.65-0.85, vs 0.86, 95% CI 0.77-0.92, respectively), with no change in specificity [21,22].

Next-Generation Sequencing

Recently, NGS has proven to be efficacious in diagnosis of culture-negative PJIs as well. A prospective study performed by Tarabichi et al evaluated the accuracy of NGS in identifying PJIs in 78 patients undergoing revision or primary arthroplasties. NGS identified infections in 25 of the 28 cases that were considered to be PJIs by MSIS criteria (95% CI, 71.8%-97.7%), whereas cultures were only able to identify 17 cases (95% CI, 40.6%-78.5%). In cases where both cultures and NGS were positive, NGS showed a high degree of concordance to traditional cultures as well [23].

NGS has also shown high degrees of detection in synovial fluid samples. Another study conducted by Tarabichi et al analyzed 86 samples of synovial fluid from the hip or knees of patients undergoing PJI evaluation. They found that NGS had a positive result in ten samples that were culture negative. Five of these samples had elevated inflammatory biomarkers, indicating an infectious process, whereas the other five had negative inflammatory biomarkers. These results suggest that NGS may be a valuable tool for evaluating PJIs in the preoperative setting but may also be at risk for false positives [24].

In addition to diagnosing prosthetic infections, NGS may also be useful for identification of causative organisms in culture-negative PJIs [23]. Furthermore, the speed at which NGS can explore an entire genome makes it a superior alternative to PCR [25]. Although NGS has exciting potential as a powerful diagnostic tool for culture-negative PJIs, there have been limited data showing its effectiveness in diagnosing other prosthetic infections. In addition, there has been no direct comparison between the effectiveness of PCR and NGS. Finally, it is important to consider that the high sensitivity may predispose NGS to a high false-positive rate and false diagnosis of PJIs [25].

Sonication

The use of sonication to break up biofilm in prosthetic implants has been shown to increase the sensitivity of both cultures and PCR when testing for infection. A prospective study performed by Tani et al compared the sensitivity and specificity of cultures obtained from sonicated explants with conventional cultures of periprosthetic tissue in 114 patients who underwent hip and knee revisions due to PJI and aseptic loosening. Sonicated cultures had a significantly increased sensitivity when compared with conventional cultures (77.0% vs 55.7%). There were no significant differences in specificity of either detection method [26].

There are some studies suggesting that sonication of prosthesis may improve the diagnosing capacity of PCR in the diagnosis of culture-negative PJIs [27–29]. However, their statistical significance remains controversial. A recent meta-analysis of 9 studies looking at the efficacy of sonication in PCR performed by Liu et al [30] found that PCR for sonication prosthetic fluid was to have clinically acceptable diagnostic values for detecting PJIs, with a pooled sensitivity of 75% (95% CI 0.71-0.79) and specificity of 96% (95% CI 0.94-0.97) [30].

Joint Biomarkers

Inflammatory biomarkers in the blood such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and CRP, as well as synovial fluid leukocyte esterase, have been part of the 2011 MSIS criteria and the 2013 consensus group modification criteria in the diagnosis of PJIs [3,31]. The updated MSIS criteria put forth by Parvizi et al in 2018 added the presence of synovial alpha-defensin and synovial CRP as criteria for diagnosis of PJIs [4]. Synovial biomarkers such as leukocyte esterase and alpha-defensin have been shown to have high sensitivity and specificity in diagnosis of PJIs and are more specific than serum inflammatory biomarkers [32–34]. The benefits of these biomarkers are that they are faster and less invasive than traditional cultures. Biomarker assays also do not require tissue sampling and may be performed on synovial fluids, which increases the convenience of these tests in diagnosing PJIs in the preoperative setting. The major drawback of joint biomarkers is that they can only indicate the presence of infection and not its specific nature. Therefore, biomarkers are best used as a preliminary indicator of the presence or absence of joint infection. They are best followed up using diagnostic assays such as PCR, NGS, or cultures to better determine the nature of infection.

Conclusion

There are a number of methods to detect sessile microorganisms in infections following orthopedic procedures. The use of PCR in the diagnosis of culture-negative PJI has shown to be more sensitive than traditional cultures, but there are conflicting data. The use of inflammatory biomarkers in both the blood and synovial fluid is also effective but cannot characterize the nature of infection or organism involved. NGS is a new test that can determine the presence of sessile microorganisms with more precision and speed than traditional cultures. Finally, sonication of explants has shown to improve the sensitivity of both cultures and PCR in diagnosing prosthesis infections.

Question 2: What is the preferred type of sample (tissue, fluid, etc.) for molecular analysis in diagnosis of orthopedic infections?

Recommendation:

Several molecular methods have been developed in an effort to provide a viable culture-independent alternative for diagnosis of orthopedic infections. However, due to the variation between studies with respect to the techniques and variety of samples collected, it remains difficult to recommend collection of one specimen type over another. While we cannot recommend a single molecular diagnostic test, careful assessment of the individual technique (location, volume, medium, temperature, and transport) utilized is needed for appropriate collection and yield from the corresponding samples.

Level of Evidence: Limited

Delegate Vote: Agree: 87%, Disagree: 2%, Abstain: 11% (Super Majority, Strong Consensus)

Rationale:

Identification of the infecting organism is imperative in the management of periprosthetic joint infection (PJI) [35,36]. Unfortunately, current methods, namely culture, have failed to perform at a level where the infecting organism is routinely identified, with up to half of PJIs yielding no known pathogen on microbiological culture [20,37–40]. Several molecular techniques have been examined to address this issue; however, no single technique has

established itself to be superior to others. Furthermore, the optimal specimen type for maximizing the sensitivity and specificity of such technologies is an even greater dilemma.

Conventional cultures typically rely on synovial fluid from aspiration, when available, as well as multiple tissue samples obtained intraoperatively. Swabs have largely fallen out of favor with evidence demonstrating their lack of sensitivity and specificity [41]. Culture of sonicate fluid has shown some promise; however, conflicting results and the need for specialized equipment preclude its routine use [42].

Synovial Fluid

Synovial fluid has been studied extensively as a source material for identifying the infective organism in PJI. When successfully obtained in the preoperative setting, it may provide the surgeon with crucial information to help guide further operative management of a patient with PJI. Various studies have reported on the performance of synovial fluid–based molecular diagnostics in isolation or in parallel with other specimen types. In a study by Huan et al, samples of periprosthetic tissue, sonication fluid, and synovial fluid were collected for both culture and 16S broad-range PCR. The authors concluded that PCRs of sonication fluid and synovial fluid were significantly more sensitive than PCR of periprosthetic tissue alone, with no difference in specificity [29]. Multiple studies have shown superiority of synovial fluid PCR to conventional culture; however, these studies simply assessed synovial fluid with no direct comparison to other specimen types [19,38,43,44]. In contrast, a study comparing the combined sensitivity and specificity of joint fluid culture and serum C-reactive protein levels versus synovial fluid PCR demonstrated inferior results.

Periprosthetic Tissue

Periprosthetic tissue is a useful specimen due to its abundance, as opposed to synovial fluid which may only be present in limited quantities, if at all. A meta-analysis by Qu et al comparing tissue, synovial fluid, and sonication fluid concluded that tissue samples conferred the maximal sensitivity, whereas sonication fluid helped optimize specificity [22]. Other reports have claimed that tissue PCR is inferior to culture; however, these studies focused on a comparison between sonicate fluid culture/PCR and tissue [17,28].

Swab

Swabs have been used in a limited fashion for molecular analysis. Omar et al compared swabs sampled for 16S rRNA PCR with those sent for tissue culture and showed a higher sensitivity in favor of swab PCR compared with culture. This is the only report assessing the utility of swabs for molecular diagnosis of PJI. However, no direct comparison was made to other specimen types in this study [15].

Although 16S rRNA PCR forms the bulk of studies assessing the different specimen types, there are emerging reports of newer techniques such as next-generation sequencing that will also need to be further explored to delineate the optimal specimen type [23,24,45]. Emerging evidence suggests that the use of gauze or larger swabs that are able to potentially sample a greater intraoperative surface area may confer a better sequencing yield.

In conclusion, the optimal specimen type for molecular analysis of PJI remains unknown. There is significant heterogeneity between studies with regard to the techniques assessed as well as the samples analyzed. Careful assessment of specific techniques is advised when using these technologies as part of the diagnostic work-up.

Question 3: What is the best diagnostic method for identifying a *C. acnes* SSI/PJI?

Recommendation:

Microbiological cultures incubated for a prolonged period (up to 14 days) are currently regarded as the best diagnostic method for identifying *C. acnes*. Subculture in thioglycolate broth is believed to improve the yield of culture for *C. acnes*.

Level of Evidence: Moderate

Delegate Vote: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale:

Cutibacterium acnes is a slow-growing, anaerobic, aerotolerant, nonsporulating, gram-positive bacillus [46]. It is part of the normal microbiome of the skin and resides in deeper layers [47]. The strains isolated in cases of invasive infections (especially in relation to orthopedic implants) differ from those identified on the skin surface in their capacity to produce biofilms [48,49]. Diagnosing low-grade infection after total joint arthroplasty is often highly complex, as clinical symptomatology and diagnostic studies may conflict [50,51]. *C. acnes* is also a common contaminant of bacterial cultures; thus, the significance of recovering this organism from periprosthetic specimens is not always clear [52].

Clinical Signs and Symptoms

Diagnosis of hip and knee periprosthetic joint infection caused by *C. acnes* remains challenging. This is primarily due to its indolent nature, which results in pain and stiffness as major complaints, rather than in the more classic signs of infection [51–54].

Serum Biomarkers

Tebruegge et al found that white blood cell count was normal in 75% of orthopedic *C. acnes* infections [55], and several studies indicate that serum ESR and CRP have a low sensitivity in such low-grade infections [34,50,52,55–58]. In a study focused on *C. acnes* total knee arthroplasty (TKA) infections [53], Nodzo et al found that ESR and CRP levels were statistically lower in the *C. acnes* PJI group, as compared with *Staphylococcus aureus (S. aureus)* TKA infections (ESR: 23 mm/h vs. 56 mm/h; CRP: 2.0 mg/dL vs. 5.9 mg/dL). In a prospective study by Grosso et al [59] on 69 patients who underwent revision shoulder arthroplasty, serum IL-6 was not an effective marker for diagnosing infection.

Synovial Biomarkers

Synovial fluid leukocyte count and neutrophil percentage have been reported as having high sensitivity and specificity in diagnosing hip and knee PJI [60–62]. The utility of the proposed cutoff points in cases of low-grade infections is unknown [57,63]. In a recent study by Nodzo et al, comparing 16 TKAs due to *C. acnes* PJI with 30 *S. aureus* TKA infections [53], the authors found that the median synovial fluid WBC count in the *C. acnes* group was 19,950 cell/mm^3. This was similar to the count in their *S. aureus* group (26,250 cell/mm^3; *P*: 0.31), as was the median percentage of polymorphonuclear neutrophils in the synovial fluid (95.5% vs. 95%; respectively, *P*: 0.13).

With regard to synovial IL-6, a recent investigation found a strong association between elevated synovial fluid IL-6 level and positive *C. acnes* culture [64] in cases of shoulder PJI.

The presence of leukocyte esterase in the synovial fluid has recently been proposed as a quick and effective marker for PJI [65]. Its utility in cases of low-grade infection has not been fully investigated. In a prospective study focused on shoulder arthroplasty,

the sensitivity of leukocyte esterase was 30% and the specificity was 67%. *C. acnes* was isolated in 63% of all positive cultures.

Numerous studies posit alpha-defensin 1 (AD-1) as a valuable biomarker for diagnosis of PJI [66–69]. Although alpha-defensin has been proven useful regardless of organism type [70], its utility in cases of low-grade pathogens such as *C. acnes* is a matter of debate. In a recent prospective study by Frangiamore et al, 33 cases of painful shoulder arthroplasty were evaluated for infection [71]. They found that alpha-defensin showed a sensitivity of 63%, a specificity of 95%, and an area under the curve of 0.78 for diagnosis of shoulder PJI. Although 63% sensitivity is not ideal for detecting all infections among infected cases, they found this an improvement over other preoperative tests. They also found a strong association between alpha-defensin levels and the growth of *C. acnes,* compared with a negative culture growth. The risk of having an alpha-defensin false-negative result [72] must be taken into account in such low-grade infections, along with the fact that the alpha-defensin test does not provide information on the identity of the infectious pathogen.

In summary, the utility of serum and synovial markers in the diagnosis of *C. acnes* periprosthetic joint infection remains unclear and in need of improvement.

Culture Techniques

C. acnes is a slow-growing, fastidious bacterium, which necessitates a longer incubation period than those routinely allowed for orthopedic specimens. For a long time, *C. acnes* was underdiagnosed in bone and joint infections due to the short cultivation times routinely used in diagnostic laboratories [73–75]. In a study [53] comparing *C. acnes* TKA infections (16 cases) and *S. aureus* TKA infections (30 cases), the meantime for culture growth in the *C. acnes* group was 8.3 ± 2.0 days, whereas it took a mean of 1.8 ± 0.8 days for *S. aureus* cultures to produce results ($P < .0001$). In another study, *C. acnes* cultures became positive at 3 to 27 days after surgery; 45% of cultures were positive at one week, 86% at two weeks, 97% were positive at three weeks, and 100% were positive at four weeks, so false-negative cultures for *C. acnes* may be as a result of short incubation or inadequate number of culture samples [56]. On the other hand, prolonging the incubation beyond a point (for instance beyond 14 days) may result in a high percentage of false-positive culture results, as *C. acnes* is a common contaminant of culture in microbiology laboratories.

It is common knowledge that *C. acnes* requires more than 5 incubation days to grow if routine cultures are used [76], but the best appropriate cultivation time is a point of controversy within the scientific community. Recent studies recommend a prolonged cultivation time—up to 14 days [75,77]—however, prolonging the incubation period is costly and labor-intensive and could also increase the likelihood of detecting organisms that are not clinically relevant. A recent study suggested that 7 days of incubation should be sufficient for accurately diagnosing orthopedic implant-associated infections [78]. In this study, 96.6% of the infections were detected within 7 days; however, *C. acnes* caused only one of the 58 infections studied. However, a study by Bossard et al [74], focusing on 70 patients with *C. acnes* orthopedic infections, found that reducing cultivation time to 7 days resulted in misdiagnosis in 15 patients (21.4%). Furthermore, the study showed that prolonging cultivation time beyond 10 days did not improve sensitivity. Thus, the authors recommend 10-day cultivation followed by a blind subculture in thioglycolate broth, in cases where suspicion of *C. acnes* infection is high. They found that thioglycolate broth culture of tissue biopsy specimens showed a significant difference in median time to positivity ($P = 0.0001$) as compared with other methods. Thioglycolate broth was most effective for the isolation *C. acnes* (sensitivity 66.3% in tissue samples and 75% in bone samples) with significantly different results than those for aerobic and anaerobic agar plates (sensitivity, 5.1% and 42.1%, respectively, $P = 0.0001$).

Culture for 10 days to isolate *C. acnes* is also supported by another study by Frangiamore et al [79] evaluating shoulder arthroplasty patients. In a very recent study by Rieber et al, anaerobe culture became detectable in supplemented liver thioglycolate broth within 6 days, emphasizing the importance of using supplemented growth media to enhance detection of these pathogens [58].

There is a concern that longer incubation periods have the potential to yield false-positive results because of specimen contamination and may not be helpful for identifying true infections. In a study by Bossard et al, 61.7% of samples belonging to their no-infection group were recorded after day 7. These results are consistent with another study by Butler-Wu et al, which showed 21.7% of cases in which only one positive *C. acnes* sample labeled as no-infection became positive after day 13 [75]. The proportion of positive cultures and the timing of culture growth may help to distinguish a true-positive from a false-positive result. In a retrospective study of 46 shoulder arthroplasty revision cases in which a positive *C. acnes* culture was identified, the time to culture growth was significantly shorter in the probable true-positive culture group (P: 0.002) compared with the probable contaminant group (median 5 days vs. 9 days). Significantly fewer days to culture growth were demonstrated among cases with a higher number of positive cultures (P: 0.001) and a higher proportion of positive cultures [79]. PJI specimens (true positives) were 6.3 times more likely to have 2 culture media positive for *C. acnes* growth than specimens from nondiagnostic events, and the authors considered a single culture-positive specimen in the absence of histologic findings to be nondiagnostic and most likely representing contamination [50,75].

Recent studies have suggested an improved effectiveness of the implant sonicate fluid culturing method over conventional periprosthetic tissue culture in detecting bacteria in total knee and total hip arthroplasty patients because of its ability to disrupt biofilm membranes [80]. Such superiority in cases of *C. acnes* infection is a matter of debate. A study conducted by Piper et al [81], investigating the utility of implant sonication in 136 cases undergoing shoulder arthroplasty or resection, found that sonicate fluid culture was more sensitive than periprosthetic tissue culture for detection of definite prosthetic shoulder infection (66.7% vs. 54.5%, respectively; $P = .046$). A recent study by Portillo et al, investigating the sensitivity of sonication in 39 orthopedic implant-associated infections—including 5 cases with *C. acnes* infection—detected all five *C. acnes* infections by sonication, but only 2 by conventional tissue cultures [82]. However, other authors have not found such advantages to the use of sonication in cases of *C. acnes* PJI. In a recent study by Bossard et al, which investigated the optimum cultivation time for isolation of *C. acnes* [74], subanalysis of 35 cases with PJI caused by *C. acnes* found a 96.2% sensitivity for tissue biopsy specimens (25/26 cases) with at least 1 positive culture, as compared with sonication fluid at 46.2% (12/26). Grosso et al evaluated the utility of implant sonication fluid cultures in diagnosing periprosthetic joint infection as compared with standard culture techniques in patients undergoing revision shoulder arthroplasty [83]. They found that implant sonication fluid cultures showed no significant superiority to standard intraoperative tissue and fluid cultures in the diagnosis of infection in patients undergoing revision shoulder arthroplasty.

Molecular Techniques

In recent years, several molecular tests that can detect the presence of pathogens by evaluating the genetic trace of these

microorganisms have become available [84,85]. Such tests seem very promising, but they are also a target of ongoing criticism. One significant challenge for PCR test is its inability to distinguish clinically important infections from mere traces of dead bacteria or bacteria that are part of the normal microbiota. Culture-independent techniques as species-specific PCR or broad-range 16S rDNA PCR have been used in the diagnosis of PJI. The high sensitivity in the detection of bacterial DNA and nonviable forms (useful in case of previous antimicrobial treatment) are described among its advantages [51,86,87]. In a recent study by Morgenstern et al, synovial fluid multiplex PCR was found superior to synovial fluid culture for detection of low-virulence bacteria such as *C. acnes* and coagulase-negative staphylococci [19]. Holmes et al [85] developed a PCR-restriction fragment length polymorphism (RFLP) approach that identifies *C. acnes* in tissue specimens within a 24-hour period. This PCR-RFLP assay combines the sensitivity of PCR with the specificity of RFLP mapping to identify *C. acnes* in surgical isolates. The assay is robust and rapid, and a *C. acnes*-positive tissue specimen can be confirmed within 24 hours of sampling, facilitating treatment decision-making, targeted antibiotic therapy, and monitoring to minimize implant failure and revision surgery [88].

However, they are not exempt from limitations. The limit of detection of the target sequence can be variable for each test, and in the absence of a quantitative technique, it can be difficult to determine whether a positive signal represents contamination or a clinically relevant infection [51,86,87]. The universal PCR has difficulties in the case of polymicrobial infections, and a low sensitivity for the diagnosis of PJI has been described [20,88].

The utility of molecular techniques, although promising, remains to be explored in the setting of *C. acnes* implant-associated infections [24,85]. Another new molecular technique that is gaining popularity is the use of next-generation sequencing (NGS) for identification of infecting pathogens causing PJI [23]. Based on a recent latter study from the Rothman Institute, NGS appeared to have a promising role in the identification of infecting organisms in over 80% of culture-negative cases that included isolation of *C. acnes* in some cases. An ongoing study examining patients with shoulder pathophysiology at the same institution appears to indicate that NGS may be a better test than traditional culture for isolation of slow-growing organisms, such as *C. acnes* that result in PJI (data to be published soon).

Histologic Analysis

Frozen section histology of periprosthetic tissues has been recommended for patients undergoing revision hip or knee arthroplasty, for whom a diagnosis of periprosthetic joint infection has not been established or has not been excluded [89]. There is a concern that low-virulence organisms such as *C. acnes* could induce a less-vigorous inflammatory reaction, characterized by a lower tissue concentration of neutrophils. According to data from a study by Grosso et al, frozen sections show a low sensitivity [90] in shoulder *C. acnes* infections (50%) using the diagnostic thresholds currently recommended for revision hip and knee arthroplasty (Feldman's criteria). The authors recommend a threshold of 10 polymorphonuclear leukocytes per 5 high-power fields, which results in an increased sensitivity (73%). In other instances, such as in a comparative study by Nodzo et al [53], acute inflammation was identified in 88% of available tissue samples (14/16) in the TKA *C. acnes* infection group, as compared with 100% of samples (29/29) in the *S. aureus* group ($P = 0.05$).

Question 4: Should organisms (e.g., *Treponema spp.*, *Corynebacteria spp.*) identified through molecular or genetic testing be treated the same as the pathogens isolated by culture?

Recommendation:

No. Because of their associated poor clinical outcomes, unusual organisms resulting in infection should not be treated equivalently to a usual pathogenic organism. Identification of unusual organisms through molecular and genetic techniques should help aid in antibiotic selection in conjunction with surgery, as indicated. Because of the associated poor clinical outcomes of unusual organisms and polymicrobial infections, the results of these newer techniques should not be ignored but instead used to help inform therapeutic choices.

Level of Evidence: Limited

Delegate Vote: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

Rationale:

There are a variety of unusual organisms that can cause periprosthetic joint infections (PJIs) aside from *Staphylococcus* species. Unusual organisms represent about 4.5% of the PJIs in the United States, whereas culture-negative infections account for 18.6% [91]. Many of these uncommon organisms, in addition to the culture-negative organisms, are associated with polymicrobial PJIs [92]. To manage such patients, broad-spectrum antibiotics are often required that need tailored to the specific organisms causing the infection due to high rates of antibiotic resistance [92].

In a recent retrospective study, methicillin-resistance *Staphylococcus aureus*—related, *Pseudomonas*-, and *Proteus*-related PJIs have been associated with lower infection-free rates, which means more surgery and hospital time are required for definitive treatment [93]. Thus, aside from methicillin-resistance *S. aureus*, there are other organisms that are associated with poor PJI outcomes.

In polymicrobial PJI, clinical outcomes were reported to be poor when compared with monomicrobial or culture-negative PJI [92]. In addition, polymicrobial PJI had a higher rate of amputation (odds ratio [OR] 3.8, 95% confidence interval [CI] 1.34-10.80, $P = .012$), arthrodesis (OR 11.06, 95% CI 1.27-96.00, $P = .029$), and PJI-related mortality (OR 7.88, 95% CI 1.60-38.67, $P = .011$) compared with patients with monomicrobial PJI [92]. In such polymicrobial PJI, gram-negative organisms (OR 6.33, $P < .01$), *Enterococci* (OR 11.36, $P < .01$), *Escherichia coli* (OR 6.55, $P < .01$), and atypical organisms (OR 9.85, $P < .01$) isolation were associated with polymicrobial PJIs [92]. PJI due to gram-negative species such as *Pseudomonas aeruginosa*, *E. coli*, and *Klebsiella pneumoniae* have proved to have lower rates of therapeutic success following debridement when compared with PJI due to gram-positive organisms [94].

Fungal infection should also be recognized as an atypical organism causing PJI. Although the reports describing PJI due to fungal infection are limited, the clinical outcomes of PJI by *Candida* species were unsatisfactory. It was reported that the overall rate of mortality attributable to *Candida* PJI was 25% [95]. Multidrug-resistant gram-negative organisms, such as carbapenemase-producing *Klebsiella pneumoniae,* require aggressive medical and surgical treatment [96]. In a small case series of *Propionibacterium avidum* PJIs, debridement-retention of the prosthesis was not an effective option [97]. Similarly, although *Enterococcal* PJI is not frequent, its successful rate of treatment was reported to be low [98,99].

Because clinical outcomes can be associated with the characteristics of the causative agent, the ideal goal is to properly identify all pathogens responsible for the infection [92]. However, some of these unusual organisms can be difficult to detect or take excessive time to appropriately culture [100]. Negative culture results can pose a challenge for physicians therapeutically, for they lack vital diagnostic information such as the true identity of the causative agent(s). Recently, research has focused on newer innovative methods of infection detection and identification. At the forefront

of these new innovative techniques are molecular and genetic methods such as PCR assay. Although current molecular and genetic methods tend to have high sensitivities, their specificities are lower and therefore cannot be used as a single diagnostic test as of now [100]. However, as technologies continue to improve, more insight into the pathologic agents will likely become available allowing physicians to make more informed therapeutic decisions based on information such as the presence of antibiotic-resistant genes.

A study by Tarabichi et al examined the utility of some of the newer molecular and genetic techniques—also known as next-generation sequencing (NGS) [23]. Based on the results of their study, they were able to conclude that NGS may be a useful adjunct to aid in organism identification [23]. Although their study shows much promise, they do note that further larger studies are needed to further validate this new technology.

Although two-stage exchange arthroplasty remains the gold standard for surgical management of chronic PJIs, especially when the causative organism is a resistant microbe or produces biofilm, the emergence of new pathogen identification methods will potentially allow physicians to choose more appropriate antibiotic regimens [23,99,101]. Much research is still needed for further validation of these techniques. However, it is clear that infection secondary to unusual organisms are associated with poor clinical outcomes and therefore should be treated with some variation from standard protocols—even if that is simply a more informed antibiotic regimen choice. Information from newer molecular and genetic techniques shows much promise in aiding in diagnosis of these types of infections.

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