HK35: Is there a role for the use of molecular techniques in isolation of infective organism(s) causing periprosthetic joint infection(PJI)?

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Response/Recommendation: Yes. Molecular techniques are promising adjuncts to conventional methods for diagnosing periprosthetic joint infection (PJI) and isolating infective organisms. These techniques may be of particular benefit in culture-negative cases, when rapid pathogen identification is critical, when rare pathogens are suspected, or in high-risk patients, such as those with a history of recurrent PJI.

Level of Evidence: Moderate

Delegate Vote:

Rationale:

One of the many challenges associated with treating a periprosthetic joint infection (PJI) is making a timely and accurate diagnosis, while also identifying the causative pathogen. The use of microbial culture remains the gold standard for pathogen identification when treating a patient with a PJI. However, over the last several years, numerous studies have evaluated the diagnostic efficacy of molecular techniques, such as Next-generation sequencing (NGS) and polymerase chain reaction (PCR). Consequently, a comprehensive literature search using PubMed and Embase was conducted on October 15th, 2024. A total of 642 articles were identified. Following initial screening and after excluding duplications and abstract review, 267 articles entered the full-text screening phase. At this stage, two independent reviewers screened the full text of the included studies, and ultimately 50 articles were selected for data extraction and evaluation.

In a study by Huang et al., NGS was utilized to detect pathogens from synovial fluid of patients undergoing revision hip and knee arthroplasty for PJI. The authors found the sensitivity (95.9%) of NGS to be significantly higher than microbial culture (79.6%). Additionally, they reported that NGS identified pathogens in all 10 of their culture-negative PJI cases, as well as 15 additional pathogens from five of their culture-positive cases. However, they did note that seven pathogens identified by cultures were missed by NGS and specificity was similar compared to culture (95.2 and 95.2%, respectively) [1]. Shi et al. also found NGS to have a higher sensitivity (89.1 versus 67.4%) and the same specificity (94.7 versus 94.7%) when compared to microbial culture, while also identifying 17 potential pathogens in 14 culture-negative PJI cases [2].

The utilization of NGS for pathogen identification in culture-negative PJIs was further investigated in a prospective multi-institutional study by Goswami et al. In their cohort of 85 culture-negative patients, NGS identified opportunistic pathogens in 65.9% of cases. Additionally, they found that NGS revealed a polymicrobial infection in 91.1% of culture-negative PJI cases [3]. Mei et al. investigated the clinical value of NGS in the diagnosis of polymicrobial PJI and found this technique to have greater sensitivity (85.7 versus 57.1%) but lower specificity (60 versus100%) and accuracy (65.2 versus 91.3%) when compared to conventional culture [4]. Additional studies have also supported these findings, suggesting that NGS is more sensitive than conventional culture, useful for detecting rare and unculturable organisms, beneficial for culture-negative PJIs, and can reduce the turnaround time needed to identify a pathogen [5-22].

In contrast to the above findings, a retrospective study by Kildow et al. found culture to be more sensitive (76.9%) and specific (95.3%) than NGS (Sensitivity: 60.9%; specificity 89.9%) [23]. Similarly, Kildow et al. sought to evaluate the diagnostic accuracy of NGS in patients with antibiotic spacers prior to reimplantation and found that NGS did not provide sufficient agreement when compared with culture or MSIS criteria [24].

The type of sample used to be evaluated by NGS has also become a topic of interest. Tan et al. assessed the diagnostic value of NGS across synovial fluid, prosthetic sonicate fluid, and periprosthetic tissue among patients with PJIs and found the sensitivity (90.7%) and specificity (94.4%) of prosthetic sonicate fluid to be superior for pathogen detection when compared to synovial fluid (Sensitivity: 83.7%; Specificity: 94.4%) and periprosthetic tissue (Sensitivity: 81.4%; Specificity: 100%) [25]. These findings support prior work which has also demonstrated

NGS using sonication fluid can improve the detection rate of pathogenic organisms [26, 27]. However, in instances when an adequate sample of sonication fluid is not obtainable, or if the prosthesis is not removed, NGS of periprosthetic tissue has been shown to have a higher sensitivity (95.5%) and specificity (90.91%) than periprosthetic tissue microbial culture (sensitivity: 72.7%; specificity: 77.3%) [28].

Preoperative synovial fluid cultures can help diagnose PJI and guide antimicrobial therapy, albeit the sensitivity of culture is low when there is an inadequate sample obtained. Fang et al. sought to evaluate if NGS could detect bacteria in such instances and found that with a low volume of synovial fluid (one ml), NGS had higher sensitivity (92%) and the same specificity (91.7%) when compared to preoperative synovial fluid culture (Sensitivity: 52%; Specificity 91.7%) [29]. In another study by Fang et al., they found that the results from preoperative synovial fluid NGS could be used to guide the optimization of intraoperative cultures to increase their sensitivity, further highlighting another potential benefit of NGS in the preoperative period [30].

Zhang et al. evaluated if serologic NGS could provide diagnostic value for the detection of PJI and found that serologic NGS had a higher sensitivity (86%) and specificity (96%) when compared to bacterial culture obtained from drainage fluid (sensitivity: 47%; specificity: 95%) [31].

The effect of antibiotics on the results of NGS has also been investigated. In their series of 52 suspected patients with PJI, Yu et al. reported a higher sensitivity (69.5%) for diagnosis and pathogen detection compared to culture (23.1%) in PJI patients who had received antibiotic treatment within two weeks of sample collection [32]. Similarly, Hao et al. found NGS to have a positivity rate of 90.5% when antibiotics were discontinued more than 14 days before surgery, 96.4% when discontinued between four and 14 days before surgery, and 77.8% when discontinued between 0 and 3 days [33].

Multiple studies have also explored the diagnostic efficacy of PCR. Gardete-Hartman et al. evaluated a multiplex PCR (mPCR) based system (BioFire Joint Infection Panel, bioMérieux, France) in patients with unclear conventional microbiological results and reported a sensitivity and specificity of 41.4 and 91.1%, respectively [34]. Additionally, Esteban et al. evaluated this same technology and found that although it has 31 targets and eight antimicrobial resistance markers, the system has lower accuracy in detecting PJI in chronic cases, due to the absence of relevant targets such as *S. epidermidis* and *C. acnes* [35]. Malandin et al. compared a different automated multiplex-PCR (mPCR) (Unyvero i60, Curetis, Germany) cartridge system to optimized culture or 16s rRNA PCR and found the concordance rate of mPCR with culture to be 58.1% and the concordance rate with 16s rRNA PCR to be 70.1% [36]. Sebastian et al. evaluated 16s rRNA gene PCR of periprosthetic tissue and found it to be more sensitive (86%) than periprosthetic tissue culture (79.4%), while maintaining the same specificity (100%) as culture and also establishing the etiology of PJI in 31% of culture-negative cases [37]. Lausmann et al. investigated the utility of mPCR and found an overall sensitivity of 78.8% and specificity of 100%. Additionally, they found mPCR to have a higher accuracy (87.5%) for acute infections when compared to chronic PJI (76.9%) and noted that the results were obtained within five hours (average: one hour), whereas the mean time for cultures was 6.4 days [38]. Fang et al. analyzed RNA-based qPCR and DNA-based qPCR and reported the sensitivity and specificity of RNA-based qPCR to be 73.6 and 100%; the sensitivity and specificity of DNA-based PCR to be 81.5 and 84.8%.; and the sensitivity and specificity of culture 65.7 and 100%, while also noting these PCR methods to be beneficial in detecting bacteria after patients received antibiotics. [39] Moshirabadi et al. performed a multi-centered study utilizing PCR with the restriction fragment length polymorphism technique and found the sensitivity (97.4%) to be higher than culture (31.6%) with both techniques having 100% specificity [40].

In contrast to the above studies, some studies have not found PCR to be as efficacious [41-43]. Suda et al. found multiplex PCR to have a sensitivity of 30.8% and a specificity of 100%, which differed significantly from conventional methods in their cohort of patients [44]. Mariaux et al. evaluated if PCR analysis of sonication fluid from bone cement spacers could improve bacterial detection and help predict whether a patient will present with a persistent infection but were unable to find a benefit [45]. Fink et al. investigated the role of preoperative PCR synovial fluid analysis and reported a sensitivity and specificity of 55.6 and 82%, which was lower than the combined sensitivity (77.8%) and specificity (95.5%) of joint fluid culture and serologic CRP [46]. However, despite these findings, multiple recent studies supported the use of PCR technologies of variable sensitivity, and high specificity; mPCR has been recommended in combination with traditional culture and other molecular diagnostic technologies in certain patient populations in culture-negative scenarios, and unclear clinical scenarios [47-56].

In conclusion, the literature supports the use of molecular techniques as adjuncts to conventional methods for the isolation of infective organisms in the setting of PJI. These techniques may have particular utility in culture-negative cases, when rapid pathogen identification is needed, when rare pathogens are suspected, or in patients with a high probability of infection, such as those with a history of recurrent PJI.

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