Periprosthetic joint infections: navigating innovations and potential translation

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Periprosthetic joint infection (PJI) remains one of the most common and devastating complications following arthroplasty. As advances in surgical innovations, education, and experience in arthroplasty continue to play a key role in reducing failure modes, such as mechanical failures and wear-related issues, PJIs have become more prominent. From a materials perspective, innovations in bone cement and cementing techniques,[1] as well as the development of highly cross-linked polyethylene,[2] have contributed to improved outcomes. Furthermore, while longer-term studies are awaited to determine the durability of these results, advances in technology and surgical techniques,[3] along with the resultant improvements in precision of component positioning and preoperative planning,[4] have shown a promising trend in reducing the incidence of other failure modes, such as instability,[5] thereby making PJIs more prominent as a clinical challenge. This complication often necessitates revision surgery and long-term antibiotic treatment, leading to substantial morbidity and healthcare costs, with a recent study highlighting an in-hospital mortality rate of 3.5% among 52,286 patients treated for PJI.[6] Despite recent developments in the diagnosis and treatment of PJIs, patients often experience lasting functional deficits and a high risk of PJI recurrence, suggesting that even the "winners are losers" in this battle against PJI.[7] Balancing the latest research advances with practical clinical applications is crucial to improving outcomes for these patients.

The diagnosis of PJI is inherently complex and requires a multifaceted approach. There is no single standalone test with sufficient specificity or sensitivity to confirm or exclude the diagnosis of PJI. However, recent advances in diagnostic methods have shown the potential to enhance the reliability of PJI detection. For instance, synovial fluid neutrophil extracellular traps (SF-NETs) have emerged as a promising biomarker, potentially improving diagnostic accuracy, particularly in culture-negative and antibiotic-pretreated cases.[8] A recent study demonstrated an area under the curve (AUC) of 0.971 for SF-NETs, with sensitivity and specificity surpassing traditional markers, including ESR, CRP, synovial white blood cell count (WBC), and polymorphonuclear neutrophil percentage (PMN%).[8] In addition, some patients, such as those with rheumatoid arthritis (RA), may present additional diagnostic challenges due to underlying inflammation. In these patients, adjusted thresholds for these markers could enhance diagnostic efficacy.[9]

Additionally, a calprotectin lateral flow immunoassay has been proposed to aid in diagnosing PJI in patients who do not meet the European Bone and Joint Infection Society (EBJIS) criteria for positive infection. A calprotectin level of > 50 mg/l showed high sensitivity (96.2%), specificity (90.9%), positive predictive value (92.6%), and negative predictive value (95.2%) for diagnosing infection.[10] Nevertheless, EBJIS criteria remain the diagnostic criterion of choice. Histopathological analysis also contributes to PJI diagnosis, and it is important for orthopaedic surgeons to recognize its value. Although the number of samples (typically between three and six tissue specimens)[11] contributes to the accuracy of the diagnosis, the crucial point is ensuring that histopathology is performed as part of the diagnostic process.

Microbiological culture remains a cornerstone in the diagnosis of PJI, although its sensitivity is not always

optimal due to factors such as biofilm formation and intracellular persistence.[12] Recent efforts to optimize tissue pretreatment methods, such as tissue-mechanical homogenization (T-MH) and tissue-dithiothreitol (T-DTT) treatment, have shown promise in improving microbial detection. Fang et al[12] demonstrated that T-MH had the highest sensitivity for detecting microorganisms, and combining it with T-DTT, a method requiring no special equipment, could further enhance bacterial yield in PJI diagnosis, underscoring the role of optimizing microbiological preanalytics to improve culture results.

Molecular diagnostics, particularly next-generation sequencing (NGS), have been reported as promising adjunctive tools for diagnosing PJI, particularly in culture-negative cases. NGS can identify a broad range of pathogens by sequencing all DNA in a sample, with reported sensitivity rates up to 89% (metagenomic NGS) in such challenging cases.[13] Despite its advantages, NGS remains supplementary to traditional methods due to concerns such as false positives and lack of consistent superiority in specificity over cultures.[14] Cell-free DNA NGS (cfDNA NGS) further reduces turnaround time and detects antimicrobial resistance genes, potentially guiding more targeted treatments.[13] While promising, these technologies should complement established diagnostics, particularly in complex or inconclusive cases.

The integration of artificial intelligence (AI) into the diagnosis and management of PJI is promising. Through natural language processing (NLP), AI has shown potential in automating data extraction from electronic health records, thus enhancing diagnostic accuracy and efficiency.[15] Moreover, AI-driven predictive algorithms can help to identify patients at risk of developing PJI,[16] assisting surgeons in making informed preoperative decisions. Machine-learning models, such as artificial neural networks, have demonstrated the ability to predict PJI following revision total knee arthroplasty by analyzing a range of risk factors.[17] Additionally, AI frameworks applied to imaging methods, such as dynamic bone scintigraphy, have shown superior diagnostic performance compared to traditional methods, offering a potential tool for accurate PJI diagnosis and improving patient outcomes.[18]

The appearance and organization of bacterial biofilm on a prosthesis is a critical step in the pathogenesis of PJI. Biofilms pose a substantial challenge, often necessitating revision arthroplasty due to their resistance to eradication without surgical intervention. However, biofilm is not the sole reason for the persistence of infection. Small colony variants and intracellular persistence, which are closely linked to biofilm, also play an important role in chronic infections.[19] This issue is becoming increasingly relevant as more caution is advised regarding the use of rifampicin between stages of staged operations, as it remains one of the few antibiotics effective against intracellular staphylococci. Recent advances, however, offer a promising outlook on biofilm management. Halicin, the first antimicrobial agent identified through a deep-learning AI approach, has demonstrated effectiveness against various bacterial strains.[20] Higashihira et al[21] reported positive findings on the efficacy of halicin against *Staphylococcus aureus* biofilms on orthopaedic substrates and recommended further in vitro studies to validate these results.[21] Additionally, Lin et al[22] found that ethylenediaminetetraacetic acid-normal saline irrigation (EDTA-NS) disrupted *S. aureus* biofilms both in vivo and in vitro, even without additional antibiotic therapy. Finally, although the use of hydrogen peroxide has been largely abandoned in the UK due to risks of gas embolism, reconsidering its use in hip and knee arthroplasty has been proposed due to its benefits in combating and disrupting bacterial biofilm.[23] This could represent a further avenue in reducing the burden of biofilm in PJI.[23]

The administration of antibiotics in the treatment of PJI remains a key component of the management strategy. Recent advances in local antibiotic administration, particularly intraosseous (IO) delivery and continuous local antibiotic perfusion (CLAP), show promise in improving outcomes.

CLAP has gained attention as a delivery system for orthopaedic infections by maintaining high local concentrations of antibiotics at the site of infection for extended periods. This technique, distinct from catheter-based methods,[24] utilizes negative pressure to direct antibiotics to the infected area while minimizing dead space and mitigating systemic side effects.[25] However, recent studies indicate that high concentrations of gentamicin can negatively impact bone cell viability and mineralization potential. While gentamicin's cellular toxicity is well documented,[26] these findings highlight the need for further investigation into optimal dosage and duration to balance efficacy with cellular health.[27]

IO antibiotic delivery provides markedly higher local antibiotic concentrations compared with traditional intravenous (IV) routes, achieving ten- to 15-fold higher levels around the knee in primary arthroplasty.[28] This method enhances targeted local drug delivery and has shown potential in reducing early PJI risk in THA and TKA,[29] potentially representing a promising adjunct in managing established PJIs. Similarly, topical antibiotics, including vancomycin powder, aim to deliver high local concentrations at the surgical site. While some studies suggest a reduction in PJI risk,[30] these results are confounded by the concurrent use of antiseptic strategies such as povidone-iodine lavage. Potential antibiotic resistance and variable outcomes indicate the need for more robust evidence before recommending routine use.[30]

Extended systemic antibiotic administration has traditionally been central to PJI management. However, recent findings have suggested that adequate surgical debridement with high local concentrations of targeted antibiotics during first-stage revision surgery can achieve high success rates without prolonged systemic therapy. A review of two-stage revision hip arthroplasties showed a 91% success rate with no statistically significant effect of the duration of IV antibiotics (less than 48 hours, less than five days, or over five days).[31] The evolving landscape in PJI management emphasizes the need for tailored approaches that optimize local drug delivery while minimizing systemic toxicity.[32]

The debridement, antibiotics, and implant retention (DAIR) protocol is a key approach for managing acute PJI, aiming to retain the prosthesis and reduce morbidity. Double DAIR, or staged DAIR, has been proposed to enhance infection control through phased interventions.[33] However, the current evidence supporting its effectiveness is limited and not robust. While some observational studies suggest potential benefits,[34] these findings are not backed by high-level evidence and results across studies have been inconsistent. Infection-specific imaging advances, such as the bacteria-specific hybrid

tracer (99mTc-UBI29-41-Cy5), could offer promising support by precisely identifying infection locations, thereby improving the efficacy of debridement and infection control.[35]

Recent research underscores the complexity and scope of revision surgery for PJI, revealing that 'real-world' revision and reinfection rates are often underestimated. Resl et al[36] highlighted this issue by analyzing the German joint registry, stressing the need to appreciate the full scale of PJI and its consequences. Exchange arthroplasty, the cornerstone of surgical management for PJI, can be performed as either a single-stage or two-stage procedure. Histological analysis is widely used during the reimplantation phase of revision surgery; however, a recent study suggests that it may not reliably predict persistent infection.[37] Additionally, the type of spacer used in a two-stage exchange remains a topic of debate. Wu et al[38] reported that while both prosthetic and cement spacers are effective for treating chronic knee PJI, prosthetic spacers were associated with better range of motion and patient-reported outcome measures (PROMs). However, the single-stage approach has recently gained attention with fewer procedures, reduced morbidity and mortality, shorter hospital stays, lower healthcare costs, and comparable or even superior outcomes in select patient groups.[39,40]

Salvage procedures may become necessary in severe PJI cases where reconstruction is not feasible. In addition to traditional surgical management, bacteriophage therapy could represent a revolutionary approach for treating refractory infections. Although still in its early stages and complicated to access, recent studies have suggested promising outcomes in bone and joint infections treated with phages.[41] Further research is needed to fully understand their efficacy, but phage therapy holds the potential to greatly alter the management of severe PJIs in the future.

Recent advances in the diagnosis, management, and prevention of PJI offer promising avenues to improving patient outcomes. Continued research and the integration of innovative technologies are essential to overcoming the challenges posed by PJI. By harmonizing cutting-edge research with practical clinical applications, we can move closer to minimizing the burden of this complex and devastating complication.

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