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REVIEW

Current Status and Perspectives of Diagnosis and Treatment of Periprosthetic Joint Infection

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Abstract: Periprosthetic joint infection (PJI) is a catastrophic complication following joint replacement surgery, posing significant challenges to orthopedic surgeons. Due to the lack of a definitive diagnostic gold standard, timely treatment initiation is problematic, resulting in substantial economic burdens on patients and society. In this review, we thoroughly analyze the complexities of PJI and emphasize the importance of accurate diagnosis and effective treatment. The article specifically focuses on the advancements in diagnostic techniques, ranging from traditional pathogen culture to advanced molecular diagnostics, and discusses their role in enhancing diagnostic accuracy. Additionally, we review the latest surgical management strategies, including everything from debridement to revision surgeries. Our summary aims to provide practical information for the diagnosis and treatment of PJI and encourages further research to improve diagnostic accuracy and treatment outcomes.

Keywords: arthroplasty, periprosthetic joint infection, PJI, molecular diagnosis, pathogenesis diagnosis, antibiotic application, recurrence of infection

Introduction

Prosthetic joint infection (PJI) is a common complication following joint replacement surgery, with an incidence rate of only 1–3%, yet it often leads to disastrous consequences.[1] Approximately 15% of revision surgeries after joint replacement are due to infections (Figure 1A).[2] Furthermore, Staphylococcus aureus is the most prevalent pathogen in cases of PJI, accounting for over 60% of instances.[3] Its high virulence and propensity to recur pose significant challenges to the treatment of PJI.[3,4] The occurrence of PJI not only severely damages patients' physical and mental health but also imposes substantial economic burdens on families and the healthcare system.[5,6] It is estimated that the total cost of secondary revision surgeries for PJI is more than double that of aseptic revisions.[7] Prevention is known to be the most effective strategy for PJI, but timely and accurate diagnosis of PJI remains critical for effective treatment. The biology of the causative microorganisms and the individualized inflammatory response of the patient pose significant challenges to the accurate diagnosis of PJI. Despite the fact that authoritative organizations including the Musculoskeletal Infection Society (MSIS),[8] the European Bone and Joint Infection Society (EBJIS),[9] and the American Academy of Orthopaedic Surgeons (AAOS) have published and regularly updated numerous diagnostic criteria for periprosthetic joint infection (PJI),[10] there remains a lack of a unified, widely recognized gold standard for the accurate diagnosis of PJI.[11–14] Of course, in terms of treatment, how to avoid recurrence of infection while restoring the function of the affected limb is the ultimate goal of PJI treatment. Ongoing efforts by medical and scientific professionals have led to notable advancements in PJI diagnosis and treatment in recent years. Based on the current state of research and clinical review, this article focuses on the molecular diagnosis and pathogen detection of PJI as well as its current mainstream therapeutic strategies (Figure 1).

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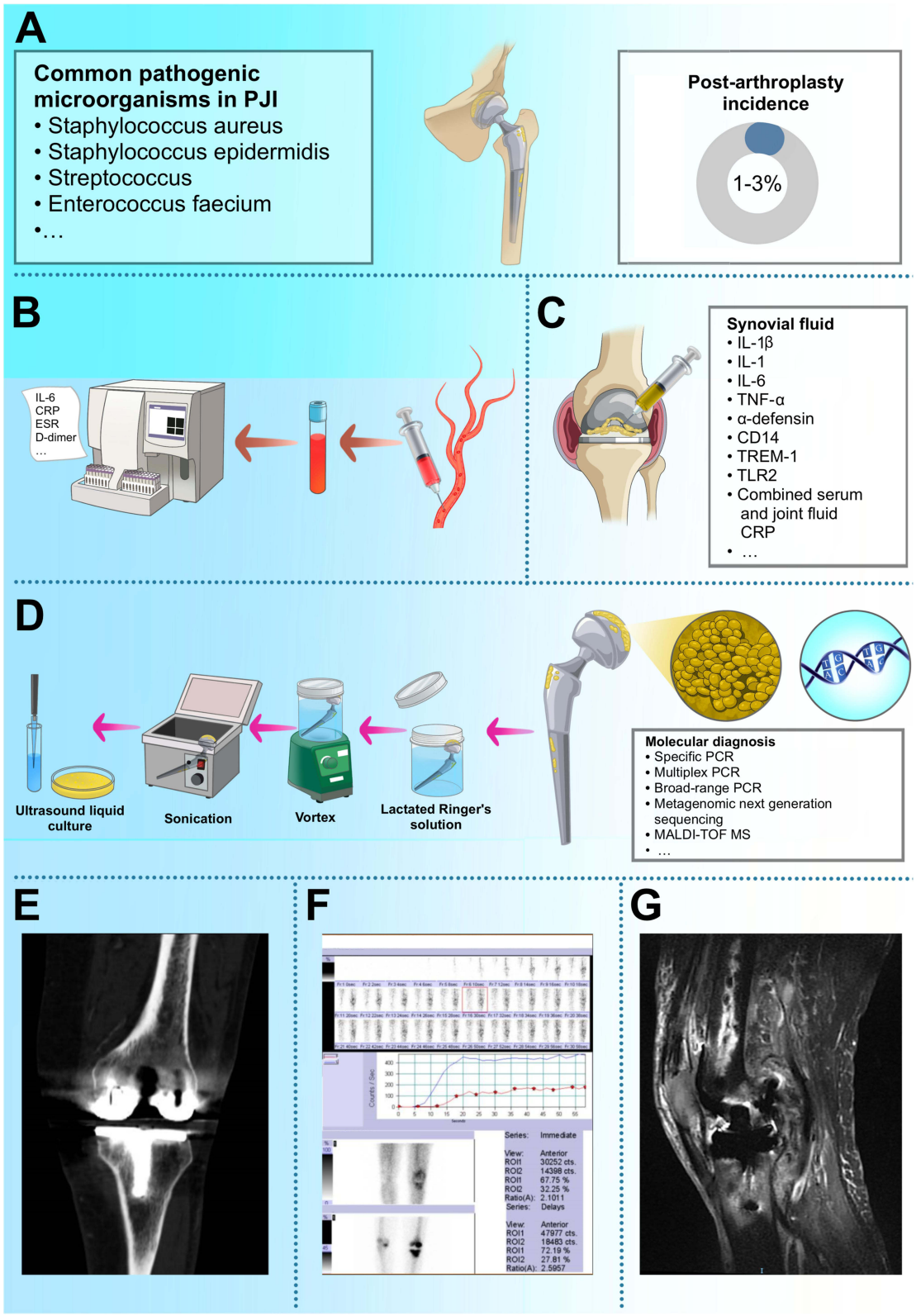

Figure 1 Diagnosis and epidemiology of Periprosthetic joint infection (PJI). (**A**) Epidemiology of PJI. (**B**) Molecular biology and Pathogen diagnosis process in PJI. (**C**) Serologic Testing of PJI. (**D**) Joint Aspiration and Synovial Fluid Analysis. (**E**–**G**) CT/ Bone Scintigraphy/MRI image of PJI patient.

Materials and Methods

In this narrative review, we utilized the criteria from the Scale for the Assessment of Narrative Review Articles (SANRA) as a standard to enhance the quality of our manuscript methodologically.[15] This article focuses on addressing several key questions: How do the latest molecular diagnostic techniques improve the detection rates of PJI? How can improvements in etiological examination methods lead to faster and more accurate identification of the pathogens responsible for PJI? What are the advancements in surgical techniques and antibiotic strategies in the management of PJI?

For our literature search, we used the following keywords: "Periprosthetic Joint Infection", "Diagnosis", "Molecular Diagnostics", "Biofilm", "Surgical Management", "Antibiotic" in the PubMed database to identify articles relevant to our topic. After rigorous relevance screening, these articles were ultimately included in our review.

Diagnosis

To enhance the accuracy of diagnosing PJI, many experts and organizations have developed a series of diagnostic criteria.[8–10] Typically, these criteria encompass blood markers (C-reactive protein, sedimentation rate, etc.), joint fluid analysis, bacterial cultures, and other specific microbiological laboratory tests. Despite these criteria and guidelines, diagnosing PJI continues to be challenging due to the limitations of existing tests, the biology of causative microorganisms, patient clinical presentation variability, and other factors. Moreover, no single test exists that can perfectly diagnose PJI.

Clinical Signs

With the continuous advancement of technology, the accuracy of laboratory diagnostics and radiological techniques for PJI has significantly improved. Nevertheless, the evaluation of associated clinical symptoms and signs remains the cornerstone for the early assessment of PJI conditions. In all relevant PJI diagnostic criteria, a sinus tract communicating with the prosthesis or joint is considered a specific clinical manifestation of PJI.[9,16] Besides focusing on the specific clinical manifestations of PJI, clinical features such as fever, erythema, swelling, pain, and joint dysfunction, although not unique to PJI, indeed increase the likelihood of infection when present.[17,18] Rapid recognition of these symptoms and prompt initiation of further evaluation are critical for achieving optimal treatment outcomes in patients with periprosthetic joint infections.

Molecular Diagnosis of Periprosthetic Joint Infection

Serologic Testing

In recent years, biomarkers have emerged as a research hotspot in PJI diagnosis research. Previously, the main serologic indicators to assist in the diagnosis were erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6), etc.[19,20] (Figure 1B) Yet, these indicators lack specificity for pathogenic infections, making it challenging for clinicians to make definitive judgments.[21] Recently, D-dimer, a product of fibrin degradation, has been identified as a promising marker for diagnosing PJI.[22] In current clinical applications, D-dimer is used to assess whether patients are hypercoagulable and to predict the risk of deep vein thrombosis in the lower extremities.[23] Fibrin can intensify the inflammatory response. Elevated D-dimer levels have been linked to infections or sepsis in patients.[8] Iskander et al noted that infection-induced endothelial cell damage leads to platelet and monocyte activation, disrupting the fibrinolytic system and potentially causing microthrombosis in microvessels, indicated by increased circulating D-dimer levels.[24] Therefore, there is a solid theoretical basis for using D-dimer as a marker to predict pathogenic infections. Pannu et al showed in a cohort analysis that serum D-dimer levels were significantly higher in patients with PJI compared to those with aseptic loosening following arthroplasty, identifying 850 ng/mL as the optimal cutoff value for PJI diagnosis.[25] Meanwhile, our study also expanded the application of D-dimer, analyzing its use in patients with common chronic PJI. We determined that the optimal threshold for diagnosing chronic PJI using D-dimer is 1170 ng/mL, with a sensitivity of 92.73% and a specificity of 74.63%.[26] In the revised 2018 PJI diagnostic criteria, D-dimer was included as a secondary adjunctive diagnostic standard.[27] However, in the current study, the diagnostic specificity of D-dimer as a novel serum marker for PJI was found to be unsatisfactory.[28] Therefore, refining the diagnostic specificity of PJI continues to be a focal point in ongoing research.

Joint Aspiration and Synovial Fluid Analysis

Preoperative arthrocentesis plays a pivotal role in diagnosing PJI. Unlike serology, joint fluid detection is distinct as serum markers can be influenced by acute or chronic inflammatory diseases in various organs and systems of the body, whereas inflammatory analysis of joint fluid, owing to its limited fluidity and containment within the joint capsule, offers a truer reflection of the local inflammatory condition (Figure 1C).[29] Preoperative synovial fluid aspiration in patients with suspected infections allows for the detection of leukocyte count and polymorphonuclear cell percentage, as well as pathogen culture.[30,31] This improves diagnostic accuracy and provides essential information for formulating targeted treatment plans.[32] Zahar et al reported that the sensitivity of synovial fluid leukocyte counts and polymorphonuclear cell percentages for diagnosis exceeds 80%, indicating substantial diagnostic value.[33] Additionally, advancements in synovial fluid research have led to the identification of numerous biomarkers.[34,35] Deirmengian et al observed that the levels of various biomarkers, including IL-1, IL-6, and Granulocyte Colony-Stimulating Factor (G-CSF), are elevated in the synovial fluid of patients with PJI, demonstrating high sensitivity and specificity.[36] These novel cytokines have significantly enhanced the diagnostic accuracy for PJI.[36] It should be noted that CRP, a commonly used serological indicator, rapidly responds to tissue injury or infection, demonstrating high sensitivity but limited specificity for localized occult infections. However, detecting CRP in joint fluid has been found to enhance its diagnostic specificity for PJI. Huang Wei's group discovered that using a combination of serum and synovial fluid CRP (serum CRP > 10.2 mg/L and synovial fluid CRP > 7.26 mg/L) to diagnose PJI achieves a sensitivity of 97.44% and a specificity of 100%. This approach not only enhances diagnostic accuracy but also reduces medical costs.[37] The test's specificity reached 100%, enhancing accuracy and reducing medical costs simultaneously. Exploration of novel molecular markers for PJI continues, including α-defensin, CD14, TREM-1, TLR2, and the CD64 index, which have shown high potential for diagnosis. Further validation through additional research is necessary.[38–40]

Molecular Biology

Although the current molecular marker diagnosis of PJI has achieved excellent results. There is still no marker that can directly confirm the diagnosis, so more scholars continue to explore new methods to accelerate and accurately diagnose PJI and identify the pathogenic organisms. Advancements in molecular biology techniques have been particularly notable (Figure 1D).

Polymerase Chain Reaction (PCR)

PCR technology plays a crucial role in the diagnosis of microbes and is extensively used in the field of PJI due to its high sensitivity and specificity.[41] This technique, by employing specially designed primers, amplifies target genes thousands to millions of times, enabling the detection of pathogen genes even at very low levels in samples. It provides a vital basis for the diagnosis of PJI. PCR can be broadly categorized into specific PCR, multiplex PCR, and broad-range PCR based on the different primers used.[42]

Specific PCR. Specific PCR designs primers for particular gene fragments of specific bacteria and amplifies them.[43] Although it has high sensitivity and specificity, the primers in the specific PCR reaction system are singular, making it difficult to screen for PJI. Therefore, it is rarely used clinically.[44]

Multiplex PCR. The principle of multiplex PCR technology is based on incorporating multiple sets of primers into the same PCR reaction system, allowing the simultaneous parallel amplification of multiple target DNA fragments in a single experiment.[44] This method can simultaneously detect a variety of common pathogenic microorganisms and their associated resistance genes (such as mecA, vanA, vanB),[45,46] greatly improving detection efficiency and specificity. It has been widely applied in the field of PJI.[47–50] Renz et al have found that multiplex PCR is particularly effective at detecting low-virulence pathogens, outperforming traditional culturing methods in identifying pathogens such as Cutibacterium spp. and coagulase-negative staphylococci.[49] Horcajada et al have applied ultrasonication to removed prosthetic components, followed by multiplex PCR on the sonicated fluid, further enhancing the sensitivity (96%) and specificity (100%) of multiplex PCR.[48] However, the limitation of multiplex PCR lies in its ability to only detect specific pathogens targeted by the primers, posing challenges in identifying PJIs caused by rare pathogens. Malandain et al also observed in a retrospective multicenter study that, of 276 culture-positive samples, only 119 (47%) were positive in

multiplex PCR, suggesting limitations in its practical application.[50] Moreover, the use of multiple primer pairs in multiplex PCR reactions can lead to primer cross-reactions and increases the complexity of setting reaction conditions.[51]

Broad-Range PCR. Broad-range PCR, which targets the highly conserved 16s rDNA gene in bacteria, simplifies the reaction system.[43] Following gene amplification, Sanger sequencing is used to identify the specific bacterial species. Patel et al have processed prosthetic components removed during revision surgeries with ultrasonication, followed by multiplex PCR, and found that broad-range PCR and culture of sonicate fluid showed similar diagnostic performance, with a sensitivity of 70.4% and specificity of 97.8% for diagnosing PJI.[52] Zhang et al in a retrospective study found that using joint fluid and sonicated fluid as samples for PCR provides higher sensitivity (83.0% and 84.9%, respectively) compared to using periprosthetic tissue (34.0%).[53] The results of broad-range PCR are often affected by various factors, including different testing samples and reagents, showing considerable variability and a higher rate of false positives. Additionally, issues such as contamination with foreign bacterial DNA can impact the accuracy of results.[54] Although current studies have methods to deal with this foreign DNA, such as using ultraviolet irradiation or reducing the number of PCR cycles, these can compromise sensitivity to some extent.[54] Therefore, the results of broad-range PCR in the diagnosis of PJI need to be carefully considered.

Recently, other techniques have been used in conjunction with PCR with good results, such as the microfluidic platform developed by Wen-Hsin Chang which allows rapid detection and typing of viable bacteria in patients' joint fluids. In addition, the microfluidic system is automated and requires little human intervention, allowing rapid diagnosis of PJI in the operating room, with potential clinical applications.[55]

Metagenomic Next Generation Sequencing

The advent of next generation sequencing technologies based on metagenomics has provided a new approach to the diagnosis of PJI. Metagenomic next generation sequencing (mNGS) refers to the sequencing of the entire DNA or RNA of a sample without the use of specific primers or probes, in comparison with microbial genetic databases.[56] The use of metagenomic next generation sequencing (mNGS) technology not only identifies the species of microorganisms that cause disease, but also detects resistance genes in these infected microorganisms, which can help joint surgeons choose more favorable treatment options. In most study, mNGS showed high diagnostic value in the diagnosis of periprosthetic tissue infections, with a high sensitivity of 95% and specificity of 90%.[57,58]

However, the presence of human nucleic acids as well as synovial microbiome in tissue-derived samples can lead to more complex data analysis by mNGS and may result in missed microbial sequences or typing errors.[59] Effective enrichment of microbial DNA will therefore be key to improving the sensitivity of macrogenomic approaches. Currently, the use of methylated CpG-specific binding protein MBD2, which is fused to human IgG Fc fragments, and the use of protein A-binding magnetic beads to selectively bind to human DNA can achieve the effect of removing human DNA. As well as the use of chaotropic reagents that selectively disrupt human cells and use DNase enzymes to degrade the DNA released from cell disruption before extracting the microbial DNA. Both of these methods help to reduce the background in the sequencing data and help to analyze the microbial DNA in a more focused manner. Matthew Thoendel used both of these methods to treat prosthetic After sonication of the fluid, it was shown that the latter was more efficient in enrichment, but may have the limitation of being difficult to apply directly on solid tissue samples again.[60]

In addition to these molecular methods, the recent advent of matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) for rapid identification of microorganisms using proteomics, as well as the development and advancement of anti-biofilm antibodies, fluorescence in situ hybridization, and gene chips have been a boon to patients with PJI. However, it is still a long time before these techniques can be implemented in most medical institutions, and the high cost of medical treatment is also a concern for healthcare professionals.[61–63]

Pathogen Detection

Tissue Culture

Culturing the pathogen in the tissue surrounding the prosthesis is the strongest evidence for the diagnosis of PJI. However, the accuracy of tissue culture is affected by the sampling method, sample type, sample size, and type of culture medium; therefore, effective avoidance of these problems during the culture process will help to increase the culture

positivity rate. Intraoperative sampling and culture is a more reliable method of identifying infectious agents than preoperative synovial fluid aspiration. In a retrospective study involving 167 incident PJIs, Nora Renz's team found that the concordance between preoperative cultures and intraoperative cultures was only 52%, and that up to 38% of cases had negative preoperative cultures but positive intraoperative cultures.[64] In addition, swab collection should be avoided when collecting samples because swabs increase the risk of cross-contamination when collecting samples and have difficulty reaching deep tissues, which can greatly interfere with the results of cultures. Austin et al, by comparing intraoperative collection of tissue samples versus swab collection of cultures in the diagnosis of PJI, found that the intraoperative sampling culture group had a sensitivity (93% versus 70%), specificity (98% versus 89%), NPV (93% versus 68%), PPV (98% versus 90%) were higher than those of the swab culture group, and also came to the same conclusions as above.[65] In addition, when collecting samples intraoperatively, four to six tissue samples should be collected from multiple sites, in order to increase the sensitivity of the culture. A prospective multicenter study recommended that best practice is to collect cultures from tissues in contact with material and joint fluid and to have the surgeon inoculate them directly into blood culture bottles, which are then sent to the laboratory for culture.[66]

However, antibiotic therapy for PJI poses a significant challenge to the traditional intraoperative culture model. Antibiotic administration reduces bacterial load and mediates bacterial dormancy leading to false-negative results. Berbari found that 53% of patients with Culture-negative PJI received antibiotic therapy prior to diagnosis of PJI.[67] Furthermore, without a definitive pathogen diagnosis, choosing the appropriate antibiotic becomes more difficult and uncertain. Therefore, in conjunction with the recommendations of the American Academy of Orthopaedic Surgeons and the Infectious Diseases Society of America practice guidelines, antibiotics should be discontinued at least 14 days prior to culturing in patients in good general condition.

Ultrasonic and Chemical Treatment of Culture

The ability of pathogens to form closed biofilms on prosthetic and bone surfaces significantly complicates traditional culture methods. Consequently, to enhance diagnostic accuracy, scientists are exploring innovative culture techniques, with sonication and chemical treatment showing promising advantages.

Ultrasonication is a method in which surgically removed implants are treated with low-frequency ultrasound and then the ultrasonicated solution is inoculated for culture. Ultrasound can directly disrupt the biofilm structure formed by pathogens and release the bacteria, thus effectively increasing the sensitivity of the culture. The most classical ultrasound method was proposed by Trampuz A.[68] The surgically removed implant was placed in a container containing 400 mL of Lactated Ringer's solution. Then, it was vortexed, sonicated, and vortexed again in sequence. The solution was then inoculated onto aerobic and anaerobic blood agar plates for culture as per tissue culture. Finally, microorganisms were counted and classified using conventional microbiological techniques (Figure 1D).[68] Optimal sensitivity 82% (76–87%), and specificity 99% (98–100%) is achieved when a threshold value ≥5 CFU is used.[69] Although several studies have now demonstrated that the sensitivity of cultures after ultrasound treatment is significantly improved in PJI compared to conventional tissue culture (61% versus 79%).[69] However, Andrew J. Brent pointed out that there are few studies comparing ultrasound treatment to the recommended 4 to 6 tissue samples or to automated culture methods that have been shown to optimize culture sensitivity. Whereas their results showed that the sensitivity of tissue culture was 69% (63–75%) better than the sensitivity of ultrasound culture 57% (50–63%), in that study, a positive ultrasound culture was placed >50 CFU/mL, and the threshold was 10 CFU/mL, which would have had some impact on the sensitivity of the culture.[70] With a deeper understanding of culture techniques, researchers have developed a variety of strategies to enhance the efficacy of sonication. Zhang et al recommend the use of the BD Bactec system for culturing sonicated samples, an improvement that can increase sensitivity to 88%.[71] Similarly, Li Cao and others found that ultrasound treatment of removed prosthetic components and their surrounding soft tissues in small metal containers directly during surgery, followed by incubation in blood culture flasks in the operating room and culturing in the BACT/ALERT 3D Blood Culture System not only increased the sensitivity rate to 91.7%, but also simplified the traditional ultrasound treatment process and reduced the risk of potential contamination.[66]

Chemical methods of treatment refer to the use of strong reducing agents such as dithiothreitol (DTT) to improve the sensitivity of the culture by destabilizing the biofilm, thereby separating the bacteria from the biofilm. Dithiothreitol is

a sulfhydryl compound, first proposed by Lorenzo Drago It can be used for the treatment of PJI samples, it can reduce the disulfide bonds of proteins in the biofilm, which will not harm the bacteria while destabilizing the biofilm's and has a high sensitivity of 85.7% and specificity of 94%.[72] The advantage of this method over ultrasonic treatment is that it does not require specialized treatment equipment and complex treatment processes. However, there is a debate about the advantages and disadvantages between chemical and ultrasonic treatments for culture, which still needs to be explored in further studies.

Imaging

Plain Radiographs

Plain films should be the imaging study of choice for evaluating the likelihood of PJI in patients. Plain films are useful in providing a reference for identifying symptomatic infectious and noninfectious conditions, such as periprosthetic fractures, prosthetic dislocation, and heterotopic ossification. The presence of an irregularly contoured translucent band around the prosthesis, loosening or displacement of the prosthesis, and destruction of the lateral bone with periosteal new bone formation are often indicative of infection when observed at an early stage. Although the sensitivity and specificity of these imaging manifestations are not high, they provide important clues, so a high degree of vigilance is still needed when confronted with these signs.[73]

CT/MRI

Computed tomography (CT) and magnetic resonance imaging (MRI) have the advantage of showing fine bony structures and accurately assessing the extent of osteolysis (Figure 1E and G). They have better sensitivity and specificity for PJI diagnosis than X-ray, but the problem of metal artifacts that cannot be completely eliminated and the high cost of detection make it difficult to clarify the additional benefits of the application of these techniques. Based on the results of the current study, there is not enough evidence to support the inclusion of CT/MRI in the diagnostic criteria for PJI.

Bone Scintigraphy

Bone scintigraphy is a technique that utilizes radioisotopes to assess the state of the bone. A 99mTc-labeled bisphosphonate compound, which is readily absorbed by new bone tissue, is typically used, followed by a triphasic bone scintigraphy scan (Figure 1F). The technique is highly sensitive to the bone remodeling process, making it extremely sensitive to PJI, and is widely used because of its rapidity and cost-effectiveness.[74] However, its specificity is low, as other pathologies such as fracture healing, aseptic loosening, and heterotopic ossification can lead to similar imaging results.

FDG-PET/CT

FDG PET can be helpful in the diagnosis of PJI based on its detection of high glucose metabolism rates in inflammatory cells and microorganisms. The technique works by injecting patients with FDG, a glucose analog that contains a radiolabeled FDG. As inflammatory cells and microorganisms in infected areas, such as PJI, have a higher rate of glucose consumption, FDG accumulates in these areas. Subsequently, signals from radioactive FDG in these areas can be captured by PET scanning, which can help physicians identify and localize the infection.[75] The advantage of FDG PET over BS is that it can provide higher quality images in a shorter period of time. However, due to the lack of harmonized standards regarding the diagnosis of PJI with FDG PET, as well as the presence of metal artifacts, and the high cost, the role of this technique in the diagnosis of PJI needs to be evaluated in further studies.

Treatment of PJI

Currently, the treatment options for PJI include sole antibiotic suppression, debridement, antibiotics and implant retention (DAIR), one-stage revision, two-stage revision, joint fusion, and amputation. Although there are numerous methods for treating PJI, there is considerable debate over the selection and effectiveness of these strategies. Antibiotic treatment serves as a cornerstone throughout the PJI treatment process. For each patient, the choice of treatment should be determined based on their individual situation and the severity of their condition.

Debridement, Antibiotics and Implant Retention (DAIR)

DAIR involves thoroughly removing non-viable tissues during surgery, excising synovial tissues and inflammatory tissues, and then repeatedly soaking and rinsing with hydrogen peroxide, iodine, and saline. Components may be replaced if necessary, while still retaining the prosthesis. After the surgery, antibiotic treatment is continued with the aim of completely eradicating pathogenic microorganisms. DAIR treatment for PJI has advantages such as low cost, simple surgical operation, short hospital stay, and the ability to retain the prosthesis while clearing the infection. A prerequisite is that the prosthesis is firmly fixed and local soft tissue conditions are good. Variability in debridement methods, perioperative management, and surgical indications across medical centers contributes to differing DAIR success rates, which range from 46% to 89%.[76] Some studies indicate that DAIR conducted within a week of infection onset can yield positive outcomes. However, the type of infecting microorganism significantly influences the success of debridement following joint replacement PJI. Specifically, DAIR's success rate falls below 30% in cases of MRSA infections.[40] Multiple factors influence DAIR's success, encompassing debridement methods, antimicrobial administration, and the patient's overall health. Thus, decision-making should not be based solely on surgery timing or symptom duration.[77] For DAIR surgery, the timing of debridement is crucial, and any delay will reduce the likelihood of successfully retaining the prosthesis. Additionally, DAIR surgery is more suitable for patients with low-virulence pathogens and no accompanying diseases. If the first debridement fails, a second attempt should be made with great caution, as the probability of failure does not diminish with subsequent attempts. Therefore, multiple debridement surgeries are generally not recommended.

Revision Surgery

Revision surgery is an effective treatment for PJI. The fundamental treatment principle is to thoroughly eradicate the infection and then reconstruct a stable and well-functioning joint. However, the optimal timing for prosthesis replacement and whether to choose a single-stage revision or the more conservative two-stage revision remain hotly debated topics..

In terms of surgical methods, a single-stage revision involves first clearing the purulent tissue around the prosthesis, then removing the original prosthesis, thoroughly debriding again, and finally implanting a new prosthesis, followed by adjunctive antibiotic treatment. In contrast, a two-stage revision involves thoroughly clearing inflammatory tissue, bone cement, and other foreign materials while removing the original prosthesis in the first stage, followed by implanting an antibiotic cement spacer and providing antibiotic treatment. After the infection is controlled, the joint replacement is done in the second stage. Compared to two-stage revisions, single-stage revisions have advantages such as fewer surgeries, shorter hospital stays, lower costs, less joint damage, quicker postoperative joint function recovery, and higher patient satisfaction.[78]

To minimize postoperative infection recurrence, it is crucial to strictly adhere to the indications and contraindications for revision surgery. Single-stage revision surgery is widely accepted under conditions where the tissues around the surgical incision are in good condition, bone loss is minimal, clear microbiological culture evidence exists, and the patient's general condition is favorable.[79] In cases lacking microbiological evidence, with multi-drug resistant or specific bacterial infections, sinus tract formation, or poor skin conditions making wound closure difficult, maximum infection control can be achieved through a two-stage revision.[80] Although two-stage revisions provide a more forgiving space and a longer anti-infection window, with advances in surgical techniques, optimization of antibiotic use, and higher demands for patient functional recovery, the indications for single-stage revisions are gradually expanding and achieving satisfactory results. Contrary to most research, studies from ENDO-Klinik suggest that single-stage revision remains a viable treatment option even in cases of recurrence of infection.[81]

Single-stage revisions generally achieve better functional recovery than two-stage revisions when infection control rates are comparable. Oussedik compared the treatment outcomes of 11 patients undergoing single-stage replacement and 39 undergoing two-stage replacement.[82] After 5 years of follow-up, both groups achieved good infection control rates. The Harris hip score (HHS) after single-stage replacement was significantly higher than that after two-stage replacement (87.8 versus 75.5). Similarly, Haddad et al compared the therapeutic effects of single-stage and two-stage revision surgeries for chronic knee PJI, finding that single-stage revisions achieved an infection control rate of 100%, compared to 93% for two-stage revisions.[83] Additionally, patients undergoing single-stage revisions recorded higher Knee Society

Scores (KSS) compared to those undergoing two-stage revisions, with scores of 88 versus 76, respectively. However, most studies on single-stage revision for PJI have issues such as small sample sizes, short follow-up periods, and lax inclusion criteria. Consequently, more clinical evidence is necessary to guide the selection of revision surgery type. Presently, two-stage revision is considered the gold standard for treating chronic PJI.[84] It's worth noting that how long one waits after the initial surgery to perform the second surgery is key to the success of a two-stage revision. But there's currently no unified standard for this waiting period. In 2013, IDSA recommended in the PJI treatment guidelines that after the one-stage spacer surgery, treatment with sensitive antibiotics should be given for 4–6 weeks before proceeding with a two-stage revision surgery.[85] Some scholars believe that during the entire transition period of the two-stage revision, the antibiotic use time should last at least 12 weeks.[86] In fact, the current debate between single-stage and two-stage revisions essentially boils down to a balance between pathogen eradication and limb function. This involves the standard procedures of debridement surgeries and the course and method of antibiotic application.

Surgical debridement involves the removal of all suspiciously infected structures in the surgical field, which will not be discussed further here. Antibiotics, as the basic safeguard for PJI treatment, are not recommended for use without surgery. Whether choosing single-stage or two-stage revision, the treatment with antibiotics deserves deep exploration. Antibiotics commonly used to treat PJI include rifampicin, vancomycin, fluoroquinolones, daptomycin, and linezolid. For PJI patients without positive bacterial culture or pending drug sensitivity results, there's no consensus on the specific choice of empirical antibiotic treatment, but vancomycin is commonly used for culture-negative cases.[87] Currently, the recommended use of antibiotics for PJI involves a combination of intravenous and oral routes. Interestingly, the infection recurrence rate due to systemic antibiotic use does not significantly differ between single-stage and two-stage revisions.[88] Consequently, given the unique structure of the joint cavity, numerous researchers have begun exploring the method of local antibiotic application. This approach significantly reduces the side effects associated with systemic antibiotic use and enhances the antimicrobial concentration at the joint site, effectively increasing the success rate of antibiotic treatment.[89] Even in patients with infections caused by multidrug-resistant pathogens, Li et al have achieved a 100% microbial cure rate through the injection of antibiotics directly into the joint cavity.[90] However, traditional antibiotic treatments still present significant limitations: 1) Long-term and uncontrolled use of antibiotics can cause serious harm to the body, such as liver and kidney failure, and hemolytic anemia; 2) Continued pressure on bacteria may promote the formation of resistant strains, thereby complicating treatment; 3) Bacteria may evade the killing effects of antibiotics through mechanisms such as biofilm formation and intracellular infection.[91–93] Therefore, these complex resistance mechanisms make the treatment of bacterial infections more challenging, and they have spurred global researchers to accelerate the development of new antibiotics and alternative treatment methods.[94–96]

Summarizing and Looking Forward

PJI, as a "catastrophic" complication following joint arthroplasty, has always been a challenge that orthopedic surgeons must overcome. Currently, issues such as molecular diagnosis of PJI, antibiotic application, and the choice of surgical methods remain the focus of research in this field. With a deeper understanding of microbiology, continuous innovations in diagnostic technology, the development of antimicrobial materials, and the optimization of antibiotic use, the clinical challenges posed by PJI will eventually be resolved. It's worth noting that for pathogens with latent infections, how to accurately identify the type of pathogen and grasp the timing and dosage of antibiotic application remain urgent clinical and research issues to tackle.

Author Contributions

Yaji Yang, Haotian Zhou, Feilong Li, Yanhao Zhang, Shenyi Dong Wei Huang, Leilei Qin conceived the study, collected the literatures, and drafted the manuscript. Corresponding authors, including Leilei Qin, Wei Huang provided their corrective comments. Wei Huang and Leilei Qin revised the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Delanois RE, Mistry JB, Gwam CU, Mohamed NS, Choksi US, Mont MA. Current epidemiology of revision total knee arthroplasty in the United States. *J Arthroplasty*. 2017;32(9):2663–2668. doi:10.1016/j.arth.2017.03.066
2. Kim HS, Park JW, Moon SY, Lee YK, Ha YC, Koo KH. Current and future burden of periprosthetic joint infection from national claim database. *J Korean Med Sci*. 2020;35(49):e410. doi:10.3346/jkms.2020.35.e410
3. Masters EA, Ricciardi BF, Bentley KLDM, Moriarty TF, Schwarz EM, Muthukrishnan G. Skeletal infections: microbial pathogenesis, immunity and clinical management. *Nat Rev Microbiol*. 2022;20(7):385–400. doi:10.1038/s41579-022-00686-0
4. Darwich A, Dally FJ, Bdeir M, et al. Delayed rifampin administration in the antibiotic treatment of periprosthetic joint infections significantly reduces the emergence of rifampin resistance. *Antibiot Basel Switz*. 2021;10(9):1139. doi:10.3390/antibiotics10091139
5. Zardi EM, Franceschi F. Prosthetic joint infection. A relevant public health issue. *J Infect Public Health*. 2020;13(12):1888–1891. doi:10.1016/j.jiph.2020.09.006
6. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty*. 2012;27(8 Suppl):61–65.e1. doi:10.1016/j.arth.2012.02.022
7. Yao JJ, Hevesi M, Visscher SL, et al. Direct inpatient medical costs of operative treatment of periprosthetic hip and knee infections are twofold higher than those of aseptic revisions. *J Bone Joint Surg Am*. 2021;103(4):312–318. doi:10.2106/JBJS.20.00550
8. P J, Tl T, G K, et al. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. *J Arthroplasty*. 2018;33(5). doi:10.1016/j.arth.2018.02.078
9. McNally M, Sousa R, Wouthuyzen-Bakker M, et al. The EBJIS definition of periprosthetic joint infection. *Bone Jt J*. 2021;103-B(1):18–25. doi:10.1302/0301-620X.103B1.BJJ-2020-1381.R1
10. Tubb CC, Polkowksi GG, Krause B. Diagnosis and prevention of periprosthetic joint infections. *J Am Acad Orthop Surg*. 2020;28(8):e340. doi:10.5435/JAAOS-D-19-00405
11. Guan H, Fu J, Li X, et al. The 2018 new definition of periprosthetic joint infection improves the diagnostic efficiency in the Chinese population. *J Orthop Surg*. 2019;14(1):151. doi:10.1186/s13018-019-1185-y
12. Sousa R, Ribau A, Alfaro P, et al. The European Bone and Joint Infection Society definition of periprosthetic joint infection is meaningful in clinical practice: a multicentric validation study with comparison with previous definitions. *Acta Orthop*. 2023;94:8–18. doi:10.2340/17453674.2023.5670
13. George J, Kwiecien G, Klika AK, et al. Are frozen sections and MSIS criteria reliable at the time of reimplantation of two-stage revision arthroplasty? *Clin Orthop*. 2016;474(7):1619–1626. doi:10.1007/s11999-015-4673-3
14. Frangiamore SJ, Siqueira MBP, Saleh A, Daly T, Higuera CA, Barsoum WK. Synovial cytokines and the MSIS criteria are not useful for determining infection resolution after periprosthetic joint infection explantation. *Clin Orthop*. 2016;474(7):1630–1639. doi:10.1007/s11999-016-4710-x
15. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev*. 2019;4:5. doi:10.1186/s41073-019-0064-8
16. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis off Publ Infect Dis Soc Am*. 2013;56(1):e1–e25. doi:10.1093/cid/cis803
17. Garlito-Díaz H, Esteban J, Mediero A, et al. A new antifungal-loaded sol-gel can prevent candida albicans prosthetic joint infection. *Antibiotics*. 2021;10(6):711. doi:10.3390/antibiotics10060711
18. Shohat N, Goswami K, Tan TL, et al. Fever and erythema are specific findings in detecting infection following total knee arthroplasty. *J Bone Jt Infect*. 2019;4(2):92–98. doi:10.7150/jbji.30088
19. Hu Q, Fu Y, Tang L. Serum D-dimer as a diagnostic index of PJI and retrospective analysis of etiology in patients with PJI. *Clin Chim Acta Int J Clin Chem*. 2020;506:67–71. doi:10.1016/j.cca.2020.03.023
20. Bingham JS, Hassebrock JD, Christensen AL, Beauchamp CP, Clarke HD, Spangehl MJ. Screening for periprosthetic joint infections with ESR and CRP: the ideal cutoffs. *J Arthroplasty*. 2020;35(5):1351–1354. doi:10.1016/j.arth.2019.11.040
21. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. *Lancet*. 2016;387(10016):386–394. doi:10.1016/S0140-6736(14)61798-0
22. Shahi A, Kheir MM, Tarabichi M, Hosseinzadeh HRS, Tan TL, Parvizi J. Serum D-Dimer test is promising for the diagnosis of periprosthetic joint infection and timing of reimplantation. *J Bone Joint Surg Am*. 2017;99(17):1419–1427. doi:10.2106/JBJS.16.01395
23. Della Valle C, Parvizi J, Bauer TW, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: the diagnosis of periprosthetic joint infections of the Hip and knee. *J Bone Joint Surg Am*. 2011;93(14):1355–1357. doi:10.2106/JBJS.9314ebo
24. Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, et al. Sepsis: multiple abnormalities, heterogeneous responses, and evolving understanding. *Physiol Rev*. 2013;93(3):1247–1288. doi:10.1152/physrev.00037.2012
25. Pannu TS, Villa JM, Manrique J, Higuera CA, Riesgo AM. Paradoxical behavior of plasma d-dimer from explantation to reimplantation in a two-stage revision for periprosthetic joint infection. *J Arthroplasty*. 2022;37(8S):S977–S982. doi:10.1016/j.arth.2022.02.023
26. Qin L, Li F, Gong X, Wang J, Huang W, Hu N. Combined measurement of D-Dimer and C-reactive protein levels: highly accurate for diagnosing chronic periprosthetic joint infection. *J Arthroplasty*. 2020;35(1):229–234. doi:10.1016/j.arth.2019.08.012

27. Johnson NR, Rowe TM, Valenzeula MM, Scarola GT, Fehring TK. Do pre-reimplantation erythrocyte sedimentation rate/C-reactive protein cutoffs guide decision-making in prosthetic joint infection? Are we flying blind? *J Arthroplasty*. 2022;37(2):347–352. doi:10.1016/j.arth.2021.10.028
28. Hansrani V, Khanbhai M, McCollum C. The diagnosis and management of early deep vein thrombosis. *Adv Exp Med Biol*. 2017;906:23–31. doi:10.1007/5584_2016_103
29. Quinlan ND, Jennings JM. Joint aspiration for diagnosis of chronic periprosthetic joint infection: when, how, and what tests? *Arthroplasty Lond Engl*. 2023;5(1):43. doi:10.1186/s42836-023-00199-y
30. Yu J, Elsayed S, Sun D. A 44-year-old man with acute asymmetric polyarthritis and fever. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2017;189(25):E861–E864. doi:10.1503/cmaj.170093
31. Tan C, Howard JL, Bondy L. Prosthetic joint infection after total Hip arthroplasty caused by Lactobacillus paracasei. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2020;192(44):E1357–E1360. doi:10.1503/cmaj.201106
32. Elkins JM, Kates S, Lange J, et al. General assembly, diagnosis, definitions: proceedings of international consensus on orthopedic infections. *J Arthroplasty*. 2019;34(2S):S181–S185. doi:10.1016/j.arth.2018.09.069
33. Zahar A, Lausmann C, Cavalheiro C, et al. How reliable is the cell count analysis in the diagnosis of prosthetic joint infection? *J Arthroplasty*. 2018;33(10):3257–3262. doi:10.1016/j.arth.2018.05.018
34. Chisari E, Parvizi J. Accuracy of blood-tests and synovial fluid-tests in the diagnosis of periprosthetic joint infections. *Expert Rev Anti Infect Ther*. 2020;18(11):1135–1142. doi:10.1080/14787210.2020.1792771
35. Lee YS, Koo KH, Kim HJ, et al. Synovial fluid biomarkers for the diagnosis of periprosthetic joint infection: a systematic review and meta-analysis. *J Bone Joint Surg Am*. 2017;99(24):2077–2084. doi:10.2106/JBJS.17.00123
36. Deirmengian C, Hallab N, Tarabishy A, et al. Synovial fluid biomarkers for periprosthetic infection. *Clin Orthop*. 2010;468(8):2017–2023. doi:10.1007/s11999-010-1298-4
37. Qin L, Li X, Wang J, Gong X, Hu N, Huang W. Improved diagnosis of chronic Hip and knee prosthetic joint infection using combined serum and synovial IL-6 tests. *Bone Jt Res*. 2020;9(9):587–592. doi:10.1302/2046-3758.99.BJR-2020-0095.R1
38. Ghanem E, Parvizi J, Burnett RSJ, et al. Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. *J Bone Joint Surg Am*. 2008;90(8):1637–1643. doi:10.2106/JBJS.G.00470
39. Xie K, Qu X, Yan M. Procalcitonin and α-defensin for diagnosis of periprosthetic joint infections. *J Arthroplasty*. 2017;32(4):1387–1394. doi:10.1016/j.arth.2016.10.001
40. Marazzi MG, Randelli F, Brioschi M, et al. Presepsin: a potential biomarker of PJI? A comparative analysis with known and new infection biomarkers. *Int J Immunopathol Pharmacol*. 2018;31:394632017749356. doi:10.1177/0394632017749356
41. Fihman V, Hannouche D, Bousson V, et al. Improved diagnosis specificity in bone and joint infections using molecular techniques. *J Infect*. 2007;55(6):510–517. doi:10.1016/j.jinf.2007.09.001
42. Zhu H, Zhang H, Xu Y, Laššáková S, Korabečná M, Neužil P. PCR past, present and future. *BioTechniques*. 2020;69(4):317–325. doi:10.2144/btn-2020-0057
43. Lévy PY, Fenollar F. The role of molecular diagnostics in implant-associated bone and joint infection. *Clin Microbiol Infect off Publ Eur Soc Clin Microbiol Infect Dis*. 2012;18(12):1168–1175. doi:10.1111/1469-0691.12020
44. Hartley JC, Harris KA. Molecular techniques for diagnosing prosthetic joint infections. *J Antimicrob Chemother*. 2014;69(Suppl 1):i21–i24. doi:10.1093/jac/dku249
45. Shanmugakani RK, Fujiya Y, Akeda Y, Hamaguchi S, Hamada S, Tomono K. Rapid multiplex detection of the resistance genes mecA, vanA and vanB from Gram-positive cocci-positive blood cultures using a PCR-dipstick technique. *J Med Microbiol*. 2020;69(2):249–255. doi:10.1099/jmm.0.001159
46. Hussein RA, Al-Ouqaili MTS, Majeed YH. Detection of clarithromycin resistance and 23SrRNA point mutations in clinical isolates of Helicobacter pylori isolates: phenotypic and molecular methods. *Saudi J Biol Sci*. 2022;29(1):513–520. doi:10.1016/j.sjbs.2021.09.024
47. Kobayashi N, Procop GW, Krebs V, Kobayashi H, Bauer TW. Molecular identification of bacteria from aseptically loose implants. *Clin Orthop*. 2008;466(7):1716–1725. doi:10.1007/s11999-008-0263-y
48. Portillo ME, Salvadó M, Sorli L, et al. Multiplex PCR of sonication fluid accurately differentiates between prosthetic joint infection and aseptic failure. *J Infect*. 2012;65(6):541–548. doi:10.1016/j.jinf.2012.08.018
49. Morgenstern C, Cabric S, Perka C, Trampuz A, Renz N. Synovial fluid multiplex PCR is superior to culture for detection of low-virulent pathogens causing periprosthetic joint infection. *Diagn Microbiol Infect Dis*. 2018;90(2):115–119. doi:10.1016/j.diagmicrobio.2017.10.016
50. Malandain D, Bémer P, Leroy AG, et al. Assessment of the automated multiplex-PCR Unyvero i60 ITI® cartridge system to diagnose prosthetic joint infection: a multicentre study. *Clin Microbiol Infect off Publ Eur Soc Clin Microbiol Infect Dis*. 2018;24(1):83.e1–83.e6. doi:10.1016/j.cmi.2017.05.017
51. Hendling M, Pabinger S, Peters K, Wolff N, Conzemius R, Barišic I. Oli2go: an automated multiplex oligonucleotide design tool. *Nucleic Acids Res*. 2018;46(W1):W252–W256. doi:10.1093/nar/gky319
52. Gomez E, Cazanave C, Cunningham SA, et al. Prosthetic joint infection diagnosis using broad-range PCR of biofilms dislodged from knee and Hip arthroplasty surfaces using sonication. *J Clin Microbiol*. 2012;50(11):3501–3508. doi:10.1128/JCM.00834-12
53. Huang Z, Wu Q, Fang X, et al. Comparison of culture and broad-range polymerase chain reaction methods for diagnosing periprosthetic joint infection: analysis of joint fluid, periprosthetic tissue, and sonicated fluid. *Int Orthop*. 2018;42(9):2035–2040. doi:10.1007/s00264-018-3827-9
54. Fox JC, Ait-Khaled M, Webster A, Emery VC. Eliminating PCR contamination: is UV irradiation the answer? *J Virol Methods*. 1991;33(3):375–382. doi:10.1016/0166-0934(91)90037-z
55. Chang WH, Wang CH, Lin CL, Wu JJ, Lee MS, Lee GB. Rapid detection and typing of live bacteria from human joint fluid samples by utilizing an integrated microfluidic system. *Biosens Bioelectron*. 2015;66:148–154. doi:10.1016/j.bios.2014.11.006
56. Chiu CY, Miller SA. Clinical metagenomics. *Nat Rev Genet*. 2019;20(6):341–355. doi:10.1038/s41576-019-0113-7
57. Cai Y, Fang X, Chen Y, et al. Metagenomic next generation sequencing improves diagnosis of prosthetic joint infection by detecting the presence of bacteria in periprosthetic tissues. *Int J Infect Dis IJID off Publ Int Soc Infect Dis*. 2020;96:573–578. doi:10.1016/j.ijid.2020.05.125
58. Tan J, Liu Y, Ehnert S, et al. The effectiveness of metagenomic next-generation sequencing in the diagnosis of prosthetic joint infection: a systematic review and meta-analysis. *Front Cell Infect Microbiol*. 2022;12:875822. doi:10.3389/fcimb.2022.875822

59. Tsai JC, Casteneda G, Lee A, et al. Identification and characterization of the intra-articular microbiome in the osteoarthritic knee. *Int J Mol Sci*. 2020;21(22):8618. doi:10.3390/ijms21228618
60. Thoendel M, Jeraldo PR, Greenwood-Quaintance KE, et al. Comparison of microbial DNA enrichment tools for metagenomic whole genome sequencing. *J Microbiol Methods*. 2016;127:141–145. doi:10.1016/j.mimet.2016.05.022
61. Kuo FC, Chien CC, Lee MS, Wang JW, Lin PC, Lee CH. Rapid diagnosis of periprosthetic joint infection from synovial fluid in blood culture bottles by direct matrix-assisted laser desorption ionization time-of-flight mass spectrometry. *PLoS One*. 2020;15(9):e0239290. doi:10.1371/journal.pone.0239290
62. Lippmann T, Braubach P, Ettinger M, Kuehnel M, Laenger F, Jonigk D. Fluorescence in Situ Hybridization (FISH) for the diagnosis of periprosthetic joint infection in formalin-fixed paraffin-embedded surgical tissues. *J Bone Joint Surg Am*. 2019;101(2):e5. doi:10.2106/JBJS.18.00243
63. Shelburne SA, Musser JM. Virulence gene expression in vivo. *Curr Opin Microbiol*. 2004;7(3):283–289. doi:10.1016/j.mib.2004.04.013
64. Schulz P, Dlaska CE, Perka C, Trampuz A, Renz N. Preoperative synovial fluid culture poorly predicts the pathogen causing periprosthetic joint infection. *Infection*. 2021;49(3):427–436. doi:10.1007/s15010-020-01540-2
65. Aggarwal VK, Higuera C, Deirmengian G, Parvizi J, Austin MS. Swab cultures are not as effective as tissue cultures for diagnosis of periprosthetic joint infection. *Clin Orthop*. 2013;471(10):3196–3203. doi:10.1007/s11999-013-2974-y
66. Ji B, Aimaiti A, Wang F, et al. Intraoperative direct sonication of implants and soft tissue for the diagnosis of periprosthetic joint infection. *J Bone Joint Surg Am*. 2023. doi:10.2106/JBJS.22.00446
67. Berbari EF, Marculescu C, Sia I, et al. Culture-negative prosthetic joint infection. *Clin Infect Dis off Publ Infect Dis Soc Am*. 2007;45(9):1113–1119. doi:10.1086/522184
68. Trampuz A, Piper KE, Jacobson MJ, et al. Sonication of removed Hip and knee prostheses for diagnosis of infection. *N Engl J Med*. 2007;357(7):654–663. doi:10.1056/NEJMoa061588
69. Zhai Z, Li H, Qin A, et al. Meta-analysis of sonication fluid samples from prosthetic components for diagnosis of infection after total joint arthroplasty. *J Clin Microbiol*. 2014;52(5):1730–1736. doi:10.1128/JCM.03138-13
70. Dudareva M, Barrett L, Figtree M, et al. Sonication versus tissue sampling for diagnosis of prosthetic joint and other orthopedic device-related infections. *J Clin Microbiol*. 2018;56(12):e00688–18. doi:10.1128/JCM.00688-18
71. Shen H, Tang J, Wang Q, Jiang Y, Zhang X. Sonication of explanted prosthesis combined with incubation in BD bactec bottles for pathogen-based diagnosis of prosthetic joint infection. *J Clin Microbiol*. 2015;53(3):777–781. doi:10.1128/JCM.02863-14
72. Drago L, Signori V, De Vecchi E, et al. Use of dithiothreitol to improve the diagnosis of prosthetic joint infections. *J Orthop Res off Publ Orthop Res Soc*. 2013;31(11):1694–1699. doi:10.1002/jor.22423
73. Romanò CL, Petrosillo N, Argento G, et al. The role of imaging techniques to define a peri-prosthetic hip and knee joint infection: multidisciplinary consensus statements. *J Clin Med*. 2020;9(8):2548. doi:10.3390/jcm9082548
74. Van den Wyngaert T, Strobel K, Kampen WU, et al. The EANM practice guidelines for bone scintigraphy. *Eur J Nucl Med Mol Imaging*. 2016;43(9):1723–1738. doi:10.1007/s00259-016-3415-4
75. Jin H, Yuan L, Li C, Kan Y, Hao R, Yang J. Diagnostic performance of FDG PET or PET/CT in prosthetic infection after arthroplasty: a meta-analysis. *Q J Nucl Med Mol Imaging Off Publ Ital Assoc Nucl Med AIMN Int Assoc Radiopharmacol IAR Sect Soc Of*. 2014;58(1):85–93.
76. Wang H, Qin L, Wang J, Hu N, Huang W. Combined serum and synovial C-reactive protein tests: a valuable adjunct to the diagnosis of chronic prosthetic joint infection. *BMC Musculoskelet Disord*. 2021;22(1):670. doi:10.1186/s12891-021-04545-6
77. Qin L, Hu N, Li X, Chen Y, Wang J, Huang W. Evaluation of synovial fluid neutrophil CD64 index as a screening biomarker of prosthetic joint infection. *Bone Jt J*. 2020;102-B(4):463–469. doi:10.1302/0301-620X.102B4.BJJ-2019-1271.R1
78. Barros LH, Barbosa TA, Esteves J, Abreu M, Soares D, Sousa R. Early Debridement, antibiotics and implant retention (DAIR) in patients with suspected acute infection after Hip or knee arthroplasty - safe, effective and without negative functional impact. *J Bone Jt Infect*. 2019;4(6):300–305. doi:10.7150/jbji.39168
79. Wouthuyzen-Bakker M, Sebillotte M, Huotari K, et al. Lower success rate of débridement and implant retention in late acute versus early acute periprosthetic joint infection caused by Staphylococcus spp. results from a matched cohort study. *Clin Orthop*. 2020;478(6):1348–1355. doi:10.1097/CORR.0000000000001171
80. Duque AF, Post ZD, Lutz RW, Orozco FR, Pulido SH, Ong AC. Is there still a role for irrigation and debridement with liner exchange in acute periprosthetic total knee infection? *J Arthroplasty*. 2017;32(4):1280–1284. doi:10.1016/j.arth.2016.10.029
81. Liechti EF, Neufeld ME, Soto F, et al. Favourable outcomes of repeat one-stage exchange for periprosthetic joint infection of the hip. *Bone Jt J*. 2022;104. doi:10.1302/0301-620X.104B1.BJJ-2021-0970.R1-B(1):27-33
82. Oussedik SIS, Dodd MB, Haddad FS. Outcomes of revision total Hip replacement for infection after grading according to a standard protocol. *J Bone Joint Surg Br*. 2010;92(9):1222–1226. doi:10.1302/0301-620X.92B9.23663
83. Haddad FS, Sukeik M, Alazzawi S. Is single-stage revision according to a strict protocol effective in treatment of chronic knee arthroplasty infections? *Clin Orthop*. 2015;473(1):8–14. doi:10.1007/s11999-014-3721-8
84. Tande AJ, Patel R. Prosthetic joint infection. *Clin Microbiol Rev*. 2014;27(2):302–345. doi:10.1128/CMR.00111-13
85. Zahar A, Gehrke TA. One-stage revision for infected total hip arthroplasty. *Orthop Clin North Am*. 2016;47(1):11–18. doi:10.1016/j.ocl.2015.08.004
86. Srivastava K, Bozic KJ, Silverton C, Nelson AJ, Makhni EC, Davis JJ. Reconsidering strategies for managing chronic periprosthetic joint infection in total knee arthroplasty: using decision analytics to find the optimal strategy between one-stage and two-stage total knee revision. *J Bone Joint Surg Am*. 2019;101(1):14–24. doi:10.2106/JBJS.17.00874
87. Kunutsor SK, Whitehouse MR, Lenguerrand E, Blom AW, Beswick AD; INFORM Team. Re-infection outcomes following one- and two-stage surgical revision of infected knee prosthesis: a systematic review and meta-analysis. *PLoS One*. 2016;11(3):e0151537. doi:10.1371/journal.pone.0151537
88. Pangaud C, Ollivier M, Argenson JN. Outcome of single-stage versus two-stage exchange for revision knee arthroplasty for chronic periprosthetic infection. *EFORT Open Rev*. 2019;4(8):495–502. doi:10.1302/2058-5241.4.190003
89. Porrino J, Wang A, Moats A, Mulcahy H, Kani K. Prosthetic joint infections: diagnosis, management, and complications of the two-stage replacement arthroplasty. *Skeletal Radiol*. 2020;49(6):847–859. doi:10.1007/s00256-020-03389-w

90. Li C, Renz N, Trampuz A. Management of periprosthetic joint infection. *Hip Pelvis*. 2018;30(3):138–146. doi:10.5371/hp.2018.30.3.138
91. Al-Ouqaili MTS, Saleh RO, Amin HIM, et al. Synthesize of pluronic-based nanovesicular formulation loaded with *Pistacia atlantica* extract for improved antimicrobial efficiency. *Arab J Chem*. 2023;16(6):104704. doi:10.1016/j.arabjc.2023.104704
92. Jwair NA, Al-Ouqaili MTS, Al-Marzooq F. Inverse association between the existence of CRISPR/cas systems with antibiotic resistance, extended spectrum β-lactamase and carbapenemase production in multidrug, extensive drug and pandrug-resistant Klebsiella pneumoniae. *Antibiot Basel Switz*. 2023;12(6):980. doi:10.3390/antibiotics12060980
93. Abdelaziz AI, Tawfik AG, Rabie KA, et al. Quality of community pharmacy practice in antibiotic self-medication encounters: a simulated patient study in Upper Egypt. *Antibiot Basel Switz*. 2019;8(2):35. doi:10.3390/antibiotics8020035
94. Howden BP, Giulieri SG, Wong Fok Lung T, et al. Staphylococcus aureus host interactions and adaptation. *Nat Rev Microbiol*. 2023;21(6):380–395. doi:10.1038/s41579-023-00852-y
95. Escoll P, Mondino S, Rolando M, Buchrieser C. Targeting of host organelles by pathogenic bacteria: a sophisticated subversion strategy. *Nat Rev Microbiol*. 2016;14(1):5–19. doi:10.1038/nrmicro.2015.1
96. Singh S, Nimmagadda A, Su M, Wang M, Teng P, Cai J. Lipidated α/α-AA heterogeneous peptides as antimicrobial agents. *Eur J Med Chem*. 2018;155:398–405. doi:10.1016/j.ejmech.2018.06.006