


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).

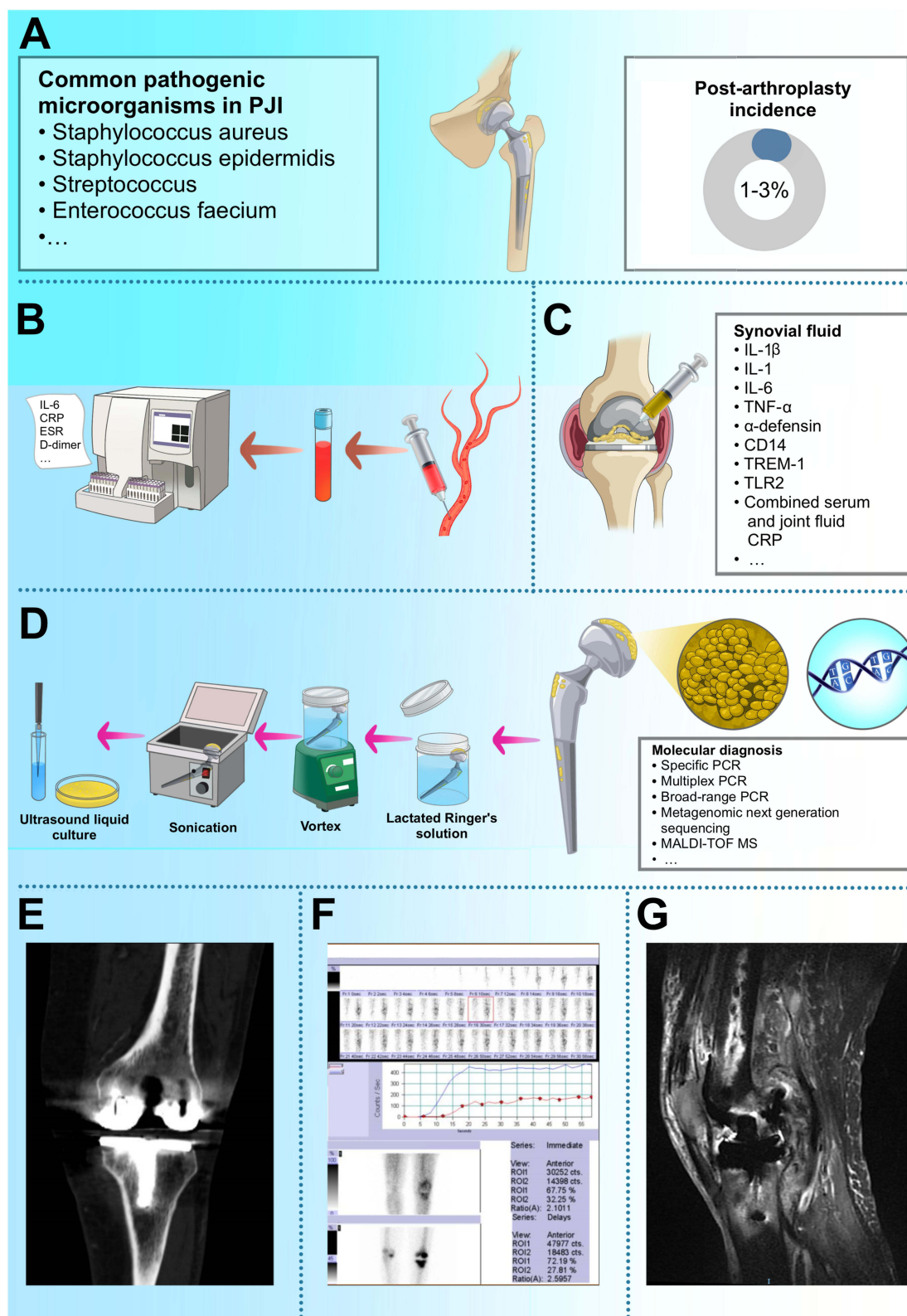


Figure 1 Diagnosis and epidemiology of Periprosthetic joint infection (PJI). **(A)** Epidemiology of PJI. **(B)** Molecular biology and Pathogen diagnosis process in PJI. **(C)** Serologic Testing of PJI. **(D)** Joint Aspiration and Synovial Fluid Analysis. **(E–G)** CT/ Bone Scintigraphy/MRI image 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 ^{99m}Tc-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.

Funding

National Postdoctoral Special Funding Project Fund (GZC20233351).

Disclosure

All of the authors declare that there are no personal, commercial, political, and any other potential conflicting interests related to the published paper.

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