CURRENT CONCEPTS REVIEW

Periprosthetic Joint Infection (PJI)

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Received: 10 August 2024 *Accepted: 22 February 2025*

Abstract

Periprosthetic joint infection (PJI) is a serious complication that can occur after joint arthroplasty, significantly affecting both the healthcare system and patients due to high costs and mortality rates. Managing PJI is complex and presents significant challenges in orthopedic surgery because there is no standardized definition for PJI and no universally accepted diagnostic gold standard. Despite various preventive measures taken before and during surgery, PJIs still occur. Many treatment options are available, but the best management is still highly debated, and the best treatment choice depends on several factors. Notably, all of these treatments are taken after the occurrence of PJI, while modern strategies, such as coating methods with various materials, must be relied upon to control and prevent the occurrence of PJI. This review focuses on the precise concept of PJIs, treatment options, and novel strategies to prevent PJIs.

Level of evidence: V

Keywords: Joint arthroplasty, Orthopedic, Periprosthetic joint infection

Introduction

Periprosthetic joint infection (PJI) is a critical complication that may arise following total joint arthroplasty (TJA) and cause failure in TJA. Also, it is reported that the PJI ranks as the third most prevalent factor for revision in total hip arthroplasty (THA).[1,2] Despite advancements in preoperative infection prevention, minimally invasive surgical techniques, silver-coated implants, and improved postoperative care, the overall incidence of PJI has not significantly decreased.[3] The PJI after TJA can lead to prolonged hospitalization, increased healthcare costs, and even implant failure accordingly; therefore, it is crucial to make a prompt and accurate diagnosis for PJI.[4] It's reported that clinical assessment, lab tests, imaging, and sometimes invasive procedures like joint aspiration or tissue sampling have key roles in diagnosing PJI. Understanding the difference between aseptic failure and infection helps choose the right treatment. Although various diagnostic criteria have been developed for PJI diagnosis, challenges still exist.[5] Various factors such as local infections and systemic sepsis substantially contribute to the development of PJI, and often permanent implant removal, fusion, amputation, or prolonged antimicrobial treatment may be required.[6,7] It is essential to acknowledge that focusing on modifiable risk factors and various surgical strategies, including preoperative screening, decolonization, antibiotic prophylaxis, and alcohol-based skin preparation solutions, can be crucial in infection prevention.[8] The current gold standard for treating PJI is implant replacement, which can be performed using one or two revision techniques.

In contrast, the Debridement, antibiotics, and implant retention (DAIR) method is an evidence-based strategy that aims to manage acute PJI without removing the implant. However, all of these treatments are implemented after the PJI has occurred. Despite various preventive measures taken before and during surgery, PJIs still occur and impose a considerable economic and health burden on patients. Therefore, new strategies must be developed and implemented to control and prevent PJI. This review focuses on the precise concept of PJIs, treatment options, and novel strategies to prevent PJIs.

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Main body

Definition and Symptoms of PJI

PJIs pose a significant clinical challenge, as there is no universally accepted definition for these infections. Their manifestations can vary widely, and traditional signs of infection, such as fever, elevated white blood cell count, and symptoms of sepsis, are often absent. Recognizing this variability is important for effective diagnosis and treatment, highlighting the necessity for enhanced awareness in this field.[9] In this regard, the suggested criteria of the Musculoskeletal Infection Society (MSIS) for PJI determination are presented in detail in the following:

1. Sinus tract connected to prosthesis
2. Observe a pathogen in at least two separate tissue or fluid samples
3. High serum Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels
4. High synovial White Blood Cells (WBC) count
5. Elevated synovial neutrophil percentage (PMN %)
6. Presence of purulence in the joint
7. Microorganism isolated in periprosthetic tissue or fluid culture
8. Over five neutrophils per high-power field in five fields

An expert clinician may also diagnose PJI if clinical suspicion is high, even if fewer than four criteria are met.[10,11] Joint pain is the most common symptom of PJI, with a range from mild to severe score.[12] Joint infections usually accompany local signs of inflammation symptoms such as redness, swelling, and warmth, but fever is not always present. In chronic cases, pain may be the only symptom of PJI, sometimes accompanied by the loosening of the prosthesis and the appearance of a draining sinus tract.[10] However, a sinus tract indicates PJI. Not all cases exhibit this symptom. In some instances, accurately distinguishing between PJI and non-infectious causes of arthroplasty failure can be challenging but is crucial for determining the appropriate treatment.[13]

Diagnostic Options

Diagnosing PJI is challenging due to the lack of gold standard tests and, therefore need to conduct a comprehensive patient history, thorough physical examination, and a range of laboratory assessments. These assessments should include synovial fluid cell counts, serum inflammatory markers, culture results, molecular techniques, and imaging techniques.[14] Serum markers like ESR and CRP can aid in diagnosing PJI because blood draws are relatively simple. However, these markers may be affected by factors such as systemic inflammation or other infections. If ESR exceeds 30 mm/hr or CRP is higher than 10 mg/L, it is important to consider the possibility of PJI. The American Academy of Orthopaedic Surgeons and the International Consensus recommend performing a joint aspirate for further evaluation when serologic tests show elevated markers. It is important to note that the serum WBC count has low sensitivity (55%) and specificity (66%) in diagnosing PJI and may not offer additional insights beyond synovial WBC testing. If ESR and CRP levels are normal, the PJI can still occur due to specific organisms such as *Corynebacterium*, *Propionibacterium acnes*, coagulase-negative *Staphylococcus*, *Candida*, *Mycobacterium*, and *Actinomyces*.[15]

Synovial fluid aspiration and culture are recommended when there is a clinical suspicion of PJI. However, prior antibiotic treatment can compromise the sensitivity of culture results, and low-virulence pathogens may go undetected.[16] A single positive culture result may be misleading, so PJI diagnosis should be considered in conjunction with other testing methods. Research by Bottner *et al*. found that CRP and Interleukin 6 (IL-6) had high sensitivity (95%) for detecting PJI, and their combined use provides an effective screening approach.[17] Procalcitonin (PCT), a serum marker elevated in bacterial infections, helps distinguish bacterial joint infections from other inflammation causes. This is crucial for directing appropriate antimicrobial therapy, potentially shortening treatment duration, and reducing the risk of resistance.[18] A study by Hugle et al. showed that PCT demonstrated higher sensitivity (93%) and specificity (75%) for septic arthritis compared to CRP at a lower cutoff level.[19] The α-defensin test, optimized and commercially available for PJI detection, shows greater sensitivity (97%) and specificity (96%) than synovial fluid CRP, with levels above 5.2 mg/ml indicative of PJI.[20] Other relevant biomarkers include cytokines such as IL-1β, IL-6, IL-8, IL-17, Tumor necrosis factor alpha (TNF-α), and Interferon-γ (IFN-γ), which are often elevated in PJI cases. Neutrophil-secreted peptides, HBD-2 and HBD-3, also promise to diagnose PJI.[21] Leukocyte esterase (LE), commonly used in urinalysis, can also be applied to synovial fluid to quickly estimate white blood cell count, offering a sensitivity of 93.3% and specificity of 77%.[22] Modern molecular diagnostic tools, such as Polymerase chain reaction (PCR), matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), and next-generation sequencing (NGS), have improved pathogen identification. PCR can detect pathogens in synovial fluid with 84% sensitivity and 89% specificity.[23] Multiplex PCR kits have effectively diagnosed bone and joint infections, with sensitivities ranging from 50% to 92%.[24] NGS also shows promising results, with a study reporting approximately 90% sensitivity for detecting PJI. A meta-analysis found high accuracy for NGS, with a pooled sensitivity of 0.93 and specificity of 0.95, highlighting its clinical diagnostic potential.[25] NGS can also offer genomic insights for predicting drug resistance and identifying multiple pathogens. While molecular techniques show promise for detecting antibiotic resistance genes, their clinical application has yet to be fully validated. At present, the cost and limited availability of these technologies restrict their use, but they have the potential to significantly improve microbial identification in the future.[26]

Etiology of PJI

PJIs are caused by a variety of bacteria and fungi. Bacterial adherence to the implant surface marks the initial stage in the development of PJI.[27] Based on the timing of occurrence, PJIs can be classified into Early PJIs (4 weeks post-arthroplasty), which are typically caused by highly virulent organisms like *Staphylococcus aureus* and beta-hemolytic *streptococci*. Delayed PJIs (3-12 months post-arthroplasty) are usually due to less virulent bacteria, such as coagulase-negative *staphylococci* and *Cutibacterium*

acnes, with *S. aureus* occurring less frequently. Late PJIs (1-2 years post-arthroplasty) are often hematogenous, with common causes including *S. aureus*, coagulase-negative *staphylococci*, and viridans *streptococci*.[13] The majority of PJIs are generated by Gram-positive cocci, *Staphylococcus aureus*, and coagulase-negative Staphylococci account for 50-60% of cases, while Streptococci and Enterococci account for 10% of cases; approximately 70% of PJIs are monomicrobial, while 25% are polymicrobial.[28]

The intracellular *staphylococci* play a key role in causing PJI by entering and surviving in host cells and letting them persist in bones for a long time by evading antibiotics and the immune system.[29] In addition, approximately 50% of PJIs are attributed to methicillin-resistant *S. aureus* (MRSA) strains. Bacterial resistance to antimicrobials is a significant factor in treatment failure.[30] In this condition, biofilms by protecting pathogens, allowing them to survive in a sessile form and contributing to the persistence of implant infections, as well as the potential to spread bacteria to other body sites.[31] The biofilms provide mechanical stability, protection from antimicrobial agents, immune cells, and retention of essential nutrients and enzymes.[32]

Host immune defenses and conventional antimicrobial therapies are frequently ineffective against bacteria within biofilms and lead to chronic inflammation.[33] Additionally, the high cell density in biofilms promotes elevated rates of horizontal gene transfer among bacteria.[34] Bacteria also evade host immunity by invading host cells, producing toxins, and altering immune responses. Different bacterial species use various strategies to evade host immune defenses. *S. aureus* has numerous mechanisms and virulence factors to escape the host immune system, including the secretion of peptides that disrupt neutrophil membranes and the activation of the agr locus in biofilms, which helps it evade neutrophil killing.[35] Additionally, it produces staphyloxanthin and superoxide dismutase to scavenge reactive oxygen species. Also, it can degrade neutrophil extracellular traps (NETs) using nucleases, which promotes macrophage cytotoxicity. Furthermore, *S. aureus* strains inhibit complement activation, enhancing their survival and allowing them to persist within neutrophils, using them to navigate through host tissues.[36]

Risk Factors Impact on PJI

Sociodemographic characteristics, body mass index (BMI), medical and surgical histories, and environmental conditions are introduced as important factors that impact the development of PJIs. Although the long-term associations between these patient-related factors and the risk of developing PJIs are not clear, identifying patients with these risk factors and reducing these risks could be crucial in decreasing the incidence of PJIs.

Reported results of the meta-analysis study indicated BMI ≥40 kg/m^2, corticosteroid therapy, low albumin levels (below 34 g/l), wound complications, a National Nosocomial Infections Surveillance (NNIS) score of 2 or higher, and any nosocomial infections as critical risk factors for PJI. Another study by Kunutsor *et al*. confirmed that various patient-related factors, such as smoking, a BMI ≥30 kg/m^2, diabetes, depression, steroid use, and frailty, are linked to increased long-term risk of developing PJIs.[37] Evidence of another meta-analysis showed factors strongly linked to PJI following shoulder arthroplasty include being male, having a prior surgical history, undergoing revision arthroplasty, experiencing acute trauma, and having preoperative osteoarthritis. The statistical analysis indicated that conditions such as diabetes mellitus, liver disease, excessive alcohol consumption, iron-deficiency anemia, and rheumatoid arthritis are associated risk factors for PJI occurring after shoulder arthroplasty.[33] Identifying patients with these risk factors who are due to have arthroplasty surgery and modulating these risk factors might be essential in reducing the incidence of PJI.

Treatment Options

The goal of treating PJI may include eradicating the infection, restoring joint functionality, alleviating symptoms, or providing palliative care through the use of suppressive antibiotics, joint fusion, and pain management. However, selecting an effective treatment method is challenging as it depends on various factors, including the infection's duration, the prosthesis's stability, the surrounding tissue's condition, and the patient's overall health. Treatment options for PJI are divided into two categories: surgical and non-surgical; non-surgical treatment primarily involves antibiotic therapy. A combination of surgical management and prolonged intravenous (IV) antibiotic courses is often recommended to optimize treatment. Surgical options include DAIR, one-stage revision, two-stage revision, and salvage procedures.[38] Each of these methods has specific advantages and disadvantages, which we will explore in detail.

Non-Surgical Option

Antibiotic Therapy

Although bacterial resistance poses significant challenges in antibiotic therapy, this method is the first approach for PJI treatment. Novel broad-spectrum antibiotics, such as daptomycin and linezolid, have been developed to address resistant infections. Daptomycin is effective against gram-positive bacteria, and Linezolid, an oxazolidinone antibiotic, is effective against resistant gram-positive bacteria, which have demonstrated over 80% success in safety and efficacy in treating staphylococcal PJI.[39] Ceftaroline, an advanced-generation cephalosporin approved in 2010, is also active against MRSA. Additionally, antibiotic therapy must consider biofilm-active agents.[40] Newly developed antibiotics, such as oritavancin and dalbavancin, provide better penetration into bone and joint tissues, which may increase their effectiveness against bacteria that form biofilms. Both antibiotics are FDA-approved and are effective against gram-positive bacteria, including meticillin-sensitive *S. aureus* (MSSA), MRSA, and vancomycin-resistant *S. aureus* (VRSA).[41] Developing novel antibiotic delivery systems, such as resorbable and non-resorbable carriers, presents a promising approach for targeting biofilm formation and improving infection eradication.[42] Bedridden or critically ill patients may need extended antibiotic therapy; however, this may not completely eradicate the infection, potentially leading to the need for lifelong treatment.[43]

Surgical Options

Debridement, Antibiotics, and Implant Retention (DAIR)

DAIR approach is generally used for early PJI with these conditions: stable implant, present symptoms for fewer than 3 weeks, no sinus tracts, and susceptible pathogen to antibiotics. In this surgical procedure, implants are fixed, the joint cavity is thoroughly cleaned, and the modular polyethylene liner components are replaced.[44] This is a recognized therapy for PJI following primary arthroplasty, demonstrating a general success rate.[45] Several factors should be considered when deciding to keep implants, including the patient's immune status, the presence of low-virulence microorganisms, and the management of biofilm within a limited timeframe. The DAIR treatment is less invasive, requires less technical skill, and leads to lower morbidity rates. It results in shorter hospital stays and better preservation of bone stock while also imposing a reduced financial burden. However, this treatment is only suitable for certain cases.[46]

One-stage Revision

One-stage revision is a preferred treatment for PJI. This procedure involves removing and replacing the infected prosthesis with new implants in a single surgery. Successful outcomes largely depend on careful patient selection, which should consider the healthy soft tissues, the extent of bone loss, and the antibiotic susceptibility of the infecting organism. In culture-negative PJIs, one-stage exchange arthroplasty may be contraindicated. Adequate viable soft tissue coverage is necessary for one-stage revision arthroplasty, and qualified surgeons must be available for flap procedures. If soft tissue coverage cannot be ensured during a one-stage exchange, a two-stage surgical approach should be considered.[47,48] The infection eradication rate for this approach now ranges from 83-89%, highlighting its effectiveness.[49] Studies have shown that one-stage revisions improve functional outcomes and higher infection-free survival rates.[50,51] The main benefit of one-stage revisions compared to two-stage revisions is that they combine the removal of the infected prosthesis and the re-implantation of a new prosthesis into one procedure. This method reduces the risks associated with undergoing multiple surgeries, shortens the duration of antibiotic treatment, leads to shorter overall hospital stays, and lowers costs along with improved patient mobilization and comparable outcomes.[52]

Two-stage Revision

The two-stage revision approach is a common and successful treatment for treating delayed and late PJIs that involves removing the infected prosthesis, inserting an antibiotic cement spacer, and re-implanting a new prosthetic joint.[49] Two-stage revision surgery has traditionally been regarded as the 'gold standard' for PJI. Numerous studies have demonstrated a successful rate of infection resolution for PJI in TKA through a two-stage revision arthroplasty method. The finding of the meta-analysis highlighted that two-stage revisions had higher success rates for infection eradication than one-stage revisions. However, the two groups had no significant difference in the microbiological profiles of the infections. These findings suggest that two-stage revisions may be more effective for treating infections.[53,54] The two-stage method is advantageous because spacers increase joint stability, prevent soft tissue contraction, and aid re-implantation procedures.[55] Two-stage revision is an effective option for patients experiencing systemic infections due to their contaminated prosthesis. An additional benefit of the two-stage exchange is its application in cases with insufficient soft tissue coverage or the presence of a sinus tract.[56,57] Nevertheless, the primary disadvantages of a two-stage exchange include longer hospital stays than one-stage revisions, possibly leading to higher costs for healthcare systems and patients. More surgical procedures elevate the risks associated with surgery for patients and the extended duration between the initial and subsequent stages leads to experience pain and instability in the knee during the interval between the two stages. Additionally, mortality rates for two-stage revision arthroplasty in patients aged over 80 years have been reported to reach as high as 36.7%. Therefore alternative salvage strategies for older patients with various health issues are required, utilizing fewer surgical interventions and modified goals.[58]

Salvage Procedures

The salvage options for complex and chronic PJI include resection arthroplasty (RA), arthrodesis, and amputation. Salvage procedures should be considered for patients with recurrent treatment failure for PJI. This is particularly important for individuals with a compromised immune system and those whose health status limits the possibility of undergoing multiple surgeries. Additionally, salvage options may be appropriate for patients not candidates for a two-stage exchange or when other surgical interventions have failed. In situations where joint function is expected to be poor after surgery, or if the infection continues despite surgical efforts, RA removing the prosthesis without replacing it should be considered option.[59] It may also be suitable for patients with deficient bone structure, compromised soft tissues, recurrent infections, or a history of unsuccessful revision surgeries.[60] RA for total knee replacement is often overlooked due to inconsistent functional outcomes. For instance, Falahee et al. reported that, while up to 89% of infections were resolved, only half of the patients could mobilize independently after surgery. This procedure is generally deemed acceptable only for those severely disabled by their infected knees before surgery.[61] RA eliminated infection in 81.5% of cases, and 59.3% of patients were satisfied with their functional outcomes.[62]

Knee arthrodesis is also a limb salvage procedure designed to stabilize the limb for weight-bearing while eliminating chronic infection in cases of recurrent PJI. The procedure involves removing all components and cement, debriding infected tissue, and using an intramedullary nail or external fixator. Relative contraindications include severe bone deficiency, significant dysfunction in adjacent joints, and extensive soft tissue loss. Complications can include delayed fusion, nonunion, and recurrent infections.[63] Above-the-knee amputation (AKA) is a last resort for treating failed TKA due

to severe PJIs. Although it can relieve pain and eradicate infection, AKA often results in poor mobility outcomes. considered for AKA, but functional decline is common, with only half achieving independent ambulation.[64]

Future Prospects in PJI Rehabilitation

The current gold standard for treating PJI is implant replacement, which can be performed using one or two revision techniques. In contrast, the DAIR method is an evidence-based strategy that aims to manage acute PJI without removing the implant. However, all of these treatments are implemented after the infection has occurred. Despite various preventive measures taken before and during surgery, PJIs still occur and impose a considerable economic and health burden on patients.[65] Therefore, new strategies must be implemented to control and prevent PJI. Currently, extensive research focuses on significant strategies to prevent and minimize complications associated with PJI. It has been suggested that implants with antimicrobial properties could present a novel strategy for preventing PJI. These strategies include surface modifications through active or passive coatings, such as silver, hydrogen, chlorine, iodine, or chromium coatings.[66] In the context of PJI, inhibiting bacterial biofilm formation has emerged as a critical prevention tactic.[67] Consequently, the implant surface has been identified as a suitable target for modifications to develop antibacterial methods.[68] Silver (Ag) is widely used in orthopedics due to its antimicrobial properties to reduce the risk of PJIs. The antimicrobial action of silver disrupts bacterial metabolism, affecting various microorganisms while presenting a low risk of developing resistance.[69] Recent studies indicate that silver-coated implants are associated with lower infection rates and a decreased need for two-stage procedures.[70] Introducing silver nanoparticles (AgNPs) further enhances effectiveness and reduces resistance due to their larger surface area and controlled release properties. However, despite the benefits of silver, high concentrations can lead to toxicity and systemic effects, including nephrotoxicity, hepatopathy, and leukopenia. Additionally, modifying surfaces with antibiotics shows promise in preventing PJIs during orthopedic surgeries. To effectively prevent PJIs, it is essential to achieve high concentrations of antibiotics with a prolonged release.[71] Modified surfaces can maintain effective antibiotic concentrations for an extended period. Key factors that influence the effectiveness of antibiotic-modified implants include the diversity of pathogens and the prevalence of antibiotic resistance, particularly concerning gentamicin and

Patients with multiple health issues are more frequently

methicillin-resistant strains.[72]

Conclusion

In conclusion, modifying coatings is an effective approach to significantly reduce the risk of PJI. Coating methods that incorporate antibiotics have proven to be successful in preventing PJIs. However, using non-antibiotic materials, such as silver and iodine, as coating agents does not effectively prevent PJIs occurrence. Despite the potential benefits of new strategies in PJI prevention, these methods are not routinely used in orthopedic surgery, and further research is needed to evaluate their effectiveness.

Acknowledgement

The authors would like to appreciate the Bone and Joint Research Laboratory, and Clinical Research Development Unit, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran for their assistance in the present manuscript.

Authors Contribution: Writing - Original Draft: Naeemeh Kalali/ Conceptualization, Supervision, Project administration: Mohammad Hosein Ebrahimzadeh/ Conceptualization, Supervision, Review & Editing: Ali Moradi/ Conceptualization, Supervision, Project administration, Review & Editing: Nafiseh Jirofti

Declaration of Conflict of Interest: The authors do NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: The authors received NO financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: N/A

Declaration of Informed Consent: N/A

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