A Clinical Review of Prosthetic Joint Infections

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KEYWORDS

• Prosthetic joint infections • Prosthetic hip infections • Prosthetic knee infections
• DAIR

KEY POINTS

- Gram-positive bacteria compose a majority of prosthetic joint infections; however, the pathogen composition can be affected by the mechanism of inoculation and timing of infection.
- Surgical management of prosthetic joint infections can include debridement, antibiotics, and implant retention, 1-stage revisions, 2-stage revisions, resection arthroplasties, arthrodesis, and amputations.
- Antimicrobial management will include an induction phase and possibly followed by chronic suppressive therapy.

PROSTHETIC JOINT INFECTIONS

Background

Prosthetic joint replacements are common surgeries for end-stage joint disease secondary to osteoarthritis, rheumatoid arthritis, and other inflammatory joint disorders. According to some studies, the prevalence of total hip and knee replacements in 2010 in the US population was 0.83% (2.5 million individuals) and 1.52% (4.7 million individuals), respectively.[1] Models suggest drastic increases by over 100% in total hip arthroplasties (THA) and total knee arthroplasties (TKA) by 2040.[2] Among many possible adverse outcomes, prosthetic joint infections (PJIs) are rarer but can be devastating. PJI incidence ranges between 1% and 2% and is a leading cause of revision arthroplasties.[3] The economic burden is projected to be $1.85 billion by 2030 for THA and TKA's.[4]

Risk factors for prosthetic joint infections include numerous patient and surgical factors. Some patient risk factors include the male gender, type II diabetes which influences wound healing, immunosuppression, malignancy, congestive heart failure,

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Abbreviations	
DAIR	debridement, antibiotics, and implant retention
EBJIS	European Bone and Joint Infection Society
IDSA	Infectious Diseases Society of America
PJI	prosthetic joint infection
THA	total hip arthroplasties
TKA	total knee arthroplasties

chronic pulmonary illnesses, preoperative anemia, depression, renal illness, increased body mass index, tobacco abuse, glucose variability postoperatively, and rheumatoid arthritis. Surgical risk factors include but are not limited to increased surgical time, bilateral arthroplasties, hospital length of stay greater than 35 days, intraarticular injections prior to TKA, and use of blood transfusions postoperatively. The incidence of infection is also higher following arthroplasty revision surgery (ie, revision for noninfectious etiology) as opposed to primary arthroplasty.[5,6]

Microbiology/Etiology

While definitions may vary, a common classification of PJIs includes early, delayed, and late prosthetic joint infections. Prosthetic join infections may arise secondary to direct pathogen inoculation during surgical intervention, contiguous spread from adjacent tissue infection, and/or hematogenous seeding.

Early prosthetic joint infections occur within 4 weeks of the primary surgery and are typically associated with inoculation during the primary surgery itself. Early PJIs are typically associated with high virulence organisms such as *Staphylococcus aureus*, aerobic gram-negative organisms, *Enterococcus* species, and certain *Streptococcal* species. Delayed PJIs occur between 3 and 12 months and are commonly associated with less virulent organisms including coagulase-negative staphylococci, viridans group streptococci, *Cutibacterium acnes*, and enterococcus species. Late PJIs occur after 1 year from surgical revision and are commonly associated with hematogenous etiology. Microbiology can vary for late PJIs.[6]

Overall, gram-positive cocci are involved in a majority of hip and knee PJIs. *S aureus* and coagulase-negative staphylococci encompass around 50% to 60% of PJIs. *Streptococci* and *Enterococcus* species contribute approximately 10% of cases while aerobic gram-negative and anaerobic bacteria such as *Cutibacterium* contribute less than 10%. Around 15% of cases are classified as culture negative.[6]

Biofilms

Biofilms play a crucial role in antibiotic resistance and treatment failure. There is an ongoing debate on whether biofilms represent a collection of individual cells or as a multicellular biological individual apart of an organism.[7] Biofilm formation starts with attachment of microbial cells to a surface, in this case the prosthesis. The lifecycle includes stages including initial growth, maturation of the biofilm, and detachment. Mature biofilms may be monomicrobial or polymicrobial but even monomicrobial biofilms may have various subpopulations with genotypic and phenotypic differences.[6] Microorganisms produce polysaccharides, proteins, and extracellular DNA to create this biofilm barrier. The biofilm will serve as protection from antimicrobials as well as the host immune system. Difficulty to eradicate the microorganisms also arises from lower growth rate within the colony, “resistant” subpopulations, and the microenvironment created. In addition, a mature biofilm has microbial cells that can communicate with each other through quorum sensing for the betterment of the biofilm as a whole.[6]

Manifestations/Diagnostics

The clinical presentation of PJI may differ based off the patient's immune status, virulence of the pathogen, and etiology of the infection. Early PJI and PJI secondary to hematogenous seeding may present with fevers, pain, erythema, and swelling to the affected joint. A sinus tract from the prothesis to the skin may form which is considered definitive criteria for a PJI. Less virulent organisms may produce less impressive symptoms, such as chronic pain, hardware loosening, and joint instability, which overlap with noninfectious conditions such as aseptic hardware failure, polyethylene wear, and adverse local tissue reaction to metal.[8]

Prosthetic joint infection diagnosis remains a clinically challenging diagnosis. Unlike native joint septic arthritis, many diagnostic criteria are quite different. Furthermore, various societies have attempted to define prosthetic joint infections with varying criteria. Infectious Diseases Society of America (IDSA) in 2012 defined PJI as having one of the following: presence of a sinus tract, presence of acute inflammation on histology, purulence surrounding the prosthesis, or positive intraoperative cultures (one positive culture of a virulent organism or multiple cultures demonstrating the same organism).[9] In 2018, the International Consensus Meeting on Musculoskeletal Infection presented updated criteria. Similarly, if a sinus tract or 2 positive cultures with the same organisms was identified, definite PJI was determined. However, PJI could also be determined using a collection of minor criteria. Minor criteria incudes evaluating C-reactive protein or D-dimer, erythrocyte sedimentation rate, a single positive culture, elevated synovial fluid white blood cell count or positive leukocyte esterase test strip or positive Alpha-defensin, elevated synovial fluid polymorphonuclear neutrophil percentage, intraoperative purulence, and positive histology. Of note, certain minor criteria have different cut off values with respect to acute and chronic PJI.[10] More recently, the European Bone and Joint Infection Society (EBJIS) published updated criteria in 2021. Infection was confirmed with sinus tract, synovial leukocyte count greater than 3000 cells/μL, synovial fluid polymorphonuclear neutrophil percentage greater than 80%, positive alpha-defensin, $\geq$ 2 positive cultures with the same organism, greater than 50 CFU/mL of any organism on sonification, presence of $\geq$5 neutrophils in high-power field histology, or presence of visible organisms on histology. Of note, they have an added category of "likely infection" based on alternative clinical findings and criteria as earlier not meeting confirmed infection.[11]

It is important to recognize that the criteria in these guidelines should guide medical decisions but not replace clinical judgment. The foresaid criteria can be affected by numerous factors including but not limited to prior antimicrobial therapy, chronicity of infection, and type of hardware present in the patient. Further muddling the diagnostic picture can be growth of organisms such as *Cutibacterium* and coagulase-negative Staphylococci which may represent contamination versus true pathogen.

Ideally, aspiration and intraoperative cultures should be taken prior to empiric antimicrobial therapy if feasible. Blood cultures should be obtained in patients with fever or systemic symptoms and where hematogenous seeding/bacteremia is suspected. Empiric antimicrobials may affect culture yield. As seen in native joint septic arthritis, preoperative antimicrobials resulted in a significant decrease in microbiologic yield.[12] With regards to PJI, it appears empiric antimicrobials affect culture yield but there is scarce literature to review.[13] When feasible, the synovial fluid should be inoculated in blood culture flasks to improve yield.[14] The IDSA recommends a minimum of 3 periprosthetic intraoperative tissue samples or prosthesis itself be sent for aerobic and anaerobic cultures.[9] In the setting of negative cultures, multiplex PCR assay may be used to assist in identification of the pathogen. If the prosthesis is removed, newer

techniques such as sonication may also be employed to improve culture yield. Sensitivities and specificities of sonication vary across studies. Aliyev and colleagues demonstrated a nonstatistical difference between sonication and traditional fluid or tissue culture yield. However, while not statistically significant, there was a trend to improved sensitivities of sonication method particularly in the setting of preoperative antibiotics.[15]

Surgical Management

Surgical management of PJI may include various options including debridement, antibiotics, and implant retention (DAIR), 1-stage revision, 2-stage revision, resection arthroplasty, arthrodesis, and amputation. DAIR and 2-stage revisions are the most common surgical interventions in the United States. The choice of surgical intervention should be approached in a multidisciplinary manner while including the patient's goals and wishes, viable surgical options, antimicrobial tolerability, surgical risks, and pathogen at hand.[8]

DAIR is a minimally invasive procedure that includes debridement of the articulation with retention of the prosthesis but commonly involves removal of mobile parts (polyethylene inserts and liners) to reduce bacterial burden. IDSA recommends that DAIR should only be attempted in settings of a well-fixed prosthesis without sinus tract who are within approximately 30 days of prosthesis implantation or fewer than 3 weeks of onset of infectious symptoms.[9] The literature reported success rates of DAIR range widely. Smaller studies report higher DAIR success rates around 60% to 80% while slightly larger cohorts and retrospective reviews detail success rates that range from 31% to 78%.[16–18] DAIR is only recommended in the above scenarios but may be implemented in other circumstances based on the overall clinical picture, surgical risks, and patient preference. While DAIR is a viable option if the above clinical criteria are met, infectious diseases consultation is recommended prior to surgical intervention as infection with certain pathogens such as *S aureus* innately carries a higher risk of failure with DAIR.[19–21]

A 1-stage revision involves the removal of the infected prosthesis. In the same surgical encounter, the joint is irrigated and debrided with the replacement of a new prosthesis. In some surgeries, surgeons may choose to exchange surgical equipment and rescrub prior to insertion of the new prosthesis.

A 2-stage revision is comprised of a first stage where prosthesis and all components are removed followed traditionally by the placement of an antibiotic cement spacer. Typically, parenteral or highly bioavailable oral antimicrobials are administered followed by an antibiotic free period. If infection is deemed to be eradicated, then a second stage of spacer removal and prosthesis reimplantation is performed. The 2-stage revisions are traditionally thought to be a more definitive treatment for PJI. While certain studies suggest DAIR and 2-stage revisions have similar success rates,[22] it is important to recognize that there are widely varying success rates in the literature which are inevitably secondary to numerous variables within the studies.

Historically, antibiotic-polymethyl methacrylate spacer blocks were employed. These antibiotic-impregnated bone cement spacers were primarily used during 2-stage revisions and would fill the dead space inside the joint cavity, provide antibiotic distribution, and restore limb length. Cement spacers can be laden with multiple antibiotics to improve the spectrum of coverage. However, these spacers were static and did not allow for joint mobility. Newer articulating spacers such as hand-made spacers, commercial preformed spacers, spacers with additional metal or polyethylene elements, autoclaved prosthesis, custom-made articulating spacers, and 3-dimensional printed spacers provide improved functional movement and improved

conditions for reimplantation.[23] With the advent of articulating spacers, an alternative surgical intervention has been more recently implemented. A 1.5-stage exchange arthroplasty involves the resection of the infected joint with the placement of an articulating spacer that remains until second-stage surgery can safely take place or remain permanently as long as the patient can tolerate it.[24] In a retrospective review of knee PJI, Hernandez and colleagues concluded that a 1.5-stage exchange arthroplasty was a viable method to treat TKA PJI. It is of note that only 16.1% of patients were placed on chronic suppressive therapy defined as being on antibiotics for greater than 6 months.[24] If a 1.5-stage exchange is performed, long-term suppressive antimicrobials may not be required.

Antimicrobial Management

While various societies may have differences regarding antimicrobial management, this article will focus on IDSA-based guidelines for the management of PJI. Starting with DAIR, there are slight differences in medical management between *Staphylococcal* versus other pathogens. In the setting of *Staphylococcal* PJI managed with DAIR, 2 to 6 weeks of pathogen-specific intravenous antimicrobial therapy in combination with rifampin followed by transition to oral antimicrobial plus rifampin for a total of 3 or 6 months for THA and TKA, respectively, is recommended (**Fig. 1**). PJI outside hips and knees are managed as THA. With regards to PJI secondary to non-*Staphylococcal* pathogens, 4 to 6 weeks of pathogen-specific parenteral or highly bioavailable oral antimicrobial therapy is recommended.[9]

If a 1-stage revision takes place, antimicrobial management is similar to that of DAIR. In *Staphylococcal* PJI managed with 1-stage exchange, 2 to 6 weeks of pathogen-specific intravenous antimicrobial therapy along with rifampin is recommended. This is followed by rifampin plus and oral companion drug for a total of 3 months (**Fig. 2**). With respect to non-staphylococcal pathogens managed with 1-stage revision, 4 to 6 weeks of pathogen-specific intravenous or highly bioavailable oral antimicrobial therapy is recommended.[9]

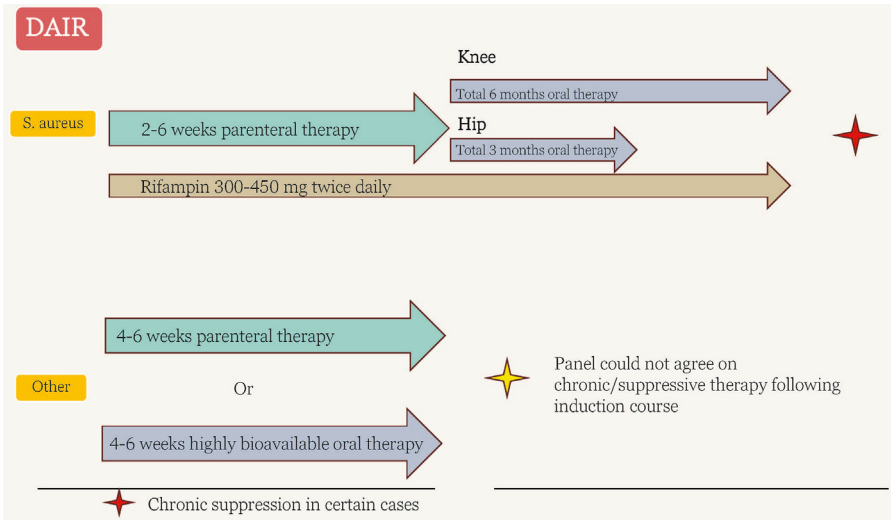

Fig. 1. *Staphylococcal* vs. other pathogen PJI managed with DAIR.

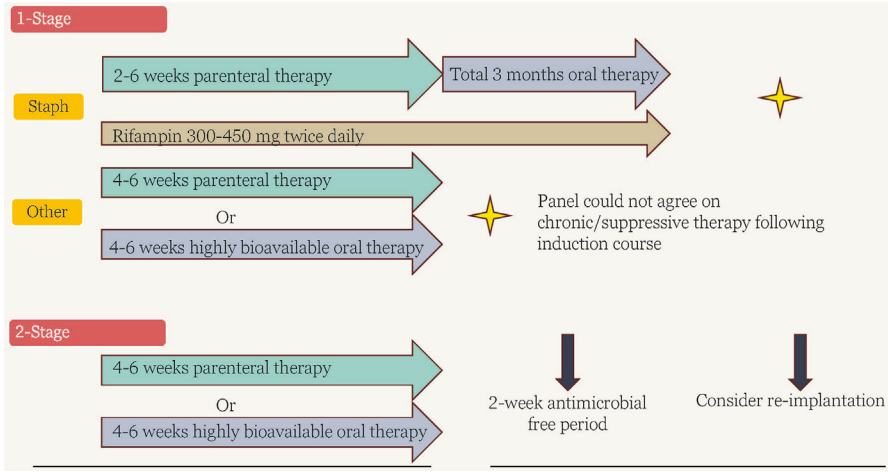

Fig. 2. *Staphylococcal* vs. other pathogen PJI managed with 1&2-stage exchange.

Medical management of 2-stage revision includes 4 to 6 weeks of pathogen-specific parenteral or highly bioavailable oral antimicrobial therapy. Typically, there is an arranged antimicrobial free period followed by further diagnostics to ensure infection is eradicated prior to prosthesis reimplantation[8,9] (see **Fig. 2**).

Finally, antimicrobial therapy following amputation as surgical intervention is dependent on the clinical syndrome. Four to 6 weeks of antimicrobial therapy may be warranted if despite surgery there is residual infected bone or infected prosthesis that may still remain.[9]

Chronic or indefinite oral antimicrobial suppressive therapy may be used in certain circumstances and is outlined in the section later.

Role of Rifampin

The role of rifampin is mainly in being an active biofilm agent. Rifampin has been demonstrated as a useful tool as an antibiofilm agent in the setting of prosthetic material.[25] It is noted that some studies do not suggest a benefit with the addition of rifampin.[26] However, most providers will use rifampin if able in the setting of *Staphylococcal* PJIs as seen in IDSA guidelines. It is important to recognize that rifampin is a drug that strongly induces cytochrome P450 (CYP) enzymes and therefore can lead to numerous drug-drug interactions.

Rifampin has a low barrier of resistance with respect to *Staphylococcal* infections. The addition of rifampin should be reserved in cases where rifampin sensitivity is demonstrated. Due to concern of the development of resistances, rifampin should only be added in appropriate cases when the burden of infection is reduced, that is, after surgical intervention and clearance of bacteremia.[27]

Chronic Suppressive Therapy

Chronic or long-term oral suppressive antimicrobial therapy is a tool commonly used by providers particularly in patients with retained hardware, that is, in DAIR surgical management. Chronic suppressive therapy is a highly debated topic and current literature leaves many unanswered questions regarding which patients to consider for chronic suppression and total duration. In many cases, the goal of chronic suppression is not necessarily aimed at eradicating the infection but rather controlling patient

symptoms and prevention of relapse of the infection. IDSA guidelines suggest considering indefinite or chronic therapy, most notably in Staphylococcal PJI infections in which patients undergo DAIR who are unsuitable or decline further surgical interventions.[9] In general, chronic suppressive therapy should be considered in patients who are at high risk for failure in the setting of retention of hardware. While most providers consider chronic suppressive therapy in the above scenario, in practice chronic therapy may be used more liberally. Nelson and colleagues listed several host, surgical/anatomic, and microbial risk factors which should heighten the consideration for using chronic suppressive therapy in DAIR. Some of these factors include advanced age, inability to tolerate further surgeries, delay in initial surgical intervention, TKA versus THA, need for repeated DAIR, difficult to treat organisms (ie, *S aureus*, enterococci, and candida), and inability to use rifampin.[8]

The use of chronic suppressive therapy should be a multidisciplinary decision between infectious diseases and orthopedic surgery along with shared decision making with the patient. The determination of whether or when to consider stopping chronic antimicrobial therapy is not clear. Horne and colleagues suggested considering cessation of chronic suppressive therapy after 1 year of continuous therapy with normalization of inflammatory markers. Though, they do warn a more cautious approach should be taken in *Staphylococcal* infections.[28]

Ultimately, the consideration to continue versus stop chronic suppressive therapy is a balance between risks and benefits with regards to possible relapse of infection versus potential ongoing adverse side effects from antimicrobial therapy. Given the paucity of knowledge with regards to suppressive therapy, more research is needed to determine patients at high risk for relapse of infection and failure rates with regards to duration of antimicrobial suppression.

SUMMARY

Prosthetic joint infections remain a challenging infection to treat. A multidisciplinary approach should be taken involving infectious disease and orthopedic specialists. Ideally, pathogen identification should help guide decisions regarding the choice of surgical intervention. The surgical approach will guide antimicrobial therapy and duration. There is a paucity of literature regarding chronic antimicrobial therapy, and further studies are needed to clarify individuals who may benefit from this approach and total duration of chronic therapy.

CLINICS CARE POINTS

- Prosthetic joint infections can be difficult to diagnose. Symptom onset and clinical picture is affected by mode of inoculation and virulence of organism.
- IDSA, ICM, and EBJIS societies outline criteria for diagnosis.
- If feasible, it is ideal to obtain presurgical cultures and operative cultures prior to empiric antimicrobial therapy.
- Prosthetic joint infections are managed by a multidisciplinary team including the primary provider, orthopedic specialist, and infectious disease specialist.
- It is ideal to have pathogen identification guide surgical management as higher virulence organisms such as *S aureus* may yield higher relapse rates in the setting of less invasive surgical intervention such as debridement, antibiotics, and implant retention (DAIR).
- DAIR should only be attempted in settings of a well-fixed prosthesis without sinus tract who are within approximately 30 days of prosthesis implantation or fewer than 3 weeks of onset of infectious symptoms.

- Antimicrobial management and duration vary based on surgical intervention.
- Chronic suppressive therapy does have possible adverse events but may be employed in certain clinical scenarios where relapse of infection is deemed higher risk.
- Literature surrounding ideal duration of chronic antimicrobial suppression is lacking and needs to be further explored.

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