

Review

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Posted Date: 17 June 2025

doi: 10.20944/preprints202506.1255.v1

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Review

Antibiotic Prophylaxis in Total Joint Arthroplasty

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Abstract: A single paragraph of about 200 words maximum. For research articles, abstracts should give a pertinent overview of the work. We strongly encourage authors to use the following style of structured abstracts, but without headings: (1) Background: Place the question addressed in a broad context and highlight the purpose of the study; (2) Methods: briefly describe the main methods or treatments applied; (3) Results: summarize the article's main findings; (4) Conclusions: indicate the main conclusions or interpretations. The abstract should be an objective representation of the article and it must not contain results that are not presented and substantiated in the main text and should not exaggerate the main conclusions.

Keywords: Periprosthetic joint infection; PJI; total knee arthroplasty; TKA; total hip arthroplasty; THA; joint replacement; infection prevention; antibiotic prophylaxis; surgical site infection; perioperative management; revision surgery; hematogenous spread; bacterial load; sterility; orthopedic surgery; infectious disease; healthcare burden; morbidity; mortality; antibiotic administration; musculoskeletal disorders; evidence-based practice; arthroplasty; clinical guidelines; perioperative care; healthcare policy

Periprosthetic joint infection (PJI) following total knee (TKA) or total hip arthroplasty (THA) is a serious condition that adversely affects patient outcomes, often leading to low satisfaction rates even after successful treatment (1). PJI significantly increases patient morbidity and mortality and is the leading cause of early revision surgery after total joint arthroplasty (2). This condition not only impacts individual patients but also places a substantial financial burden on the healthcare system (3). In the United States, the incidence of PJI varies by joint, with estimates of 1-2% for primary THA and TKA (4). The most common pathogens are Gram-positive bacteria, followed by Gram-negative bacteria and fungi (5). Typical Gram-positive pathogens include coagulase-negative staphylococci, *Staphylococcus aureus*, enterococci, streptococci and micrococci. Infections can arise from local spread from the skin or air, or through hematogenous seeding of the affected joint. It is estimated that a minimum of 10^5 bacteria per gram of tissue can cause PJI, while as few as 50 colony-forming units per milliliter in an intraoperative tissue sample are sufficient to diagnose the infection (6,7). Therefore, reducing the bacterial burden at the surgical site is crucial for preventing postoperative infections. This can be accomplished both through efforts to maintain perioperative sterility and through the use of antibiotics. Effective antibiotic administration plays a vital role in minimizing infection risk during total joint arthroplasty. Antibiotic prophylaxis has been proven to reduce the number of PJIs and is considered the gold standard in PJI prevention. There is variability and debate on what is the ideal route of antibiotic administration to prevent prosthetic joint infection in THA and TKA. We present here a brief review of the current literature and evidence on antibiotic use during primary total hip and knee replacements.

Intravenous Perioperative Antibiotic Administration

Use of intravenous (IV) perioperative antibiotics has been one of the most noteworthy interventions in the prevention of prosthetic joint infections (PJI). Evidence in support of perioperative antibiotic prophylaxis dates back to the late 1960s (8) and the practice became the standard of care decades before the Center for Disease Control and Prevention (CDC) established in

1999 perioperative antibiotic prophylaxis as a major guideline (8,9). There are several important parameters to consider in optimizing the efficacy of antibiotic prophylaxis. These include choice of antibiotic, route of administration, dosage, timing of dose, duration, side effects, and potential bacterial resistance. Antimicrobial stewardship, which is a systematic effort to support evidence-based antibiotic use, is one of the main considerations in the judicious utilization of perioperative antibiotics (10). Inappropriate antibiotic use may lead to increased adverse effects, secondary infections, drug interactions, additional costs, prolonged lengths of stay, and hospital readmissions. Furthermore, bacterial resistance may develop, which can then lead to treatment failure in confirmed cases of PJI (11,12).

While antibiotic choices vary in the literature, the American Academy of Orthopaedic Surgeons (AAOS) 2019 clinical guidelines for diagnosis and prevention of periprosthetic joint infection recommend the use of the first (cefazolin) or second (cefuroxime) generation cephalosporin, or a glycopeptide (vancomycin) (13). First and second generation cephalosporins are preferred for their adequate Gram positive and negative coverage as well as their favorable side effect profile. The current AAOS guidelines recommend a weight-based dose of 1 to 3 grams of cefazolin to be administered within 1 hour of surgical incision. The rationale for giving antibiotics within one hour of incision emerges from prior pharmacokinetic and clinical studies demonstrating that the infectious and immunologic status of a patient in the 1 hour prior to surgical incision has the greatest influence on the risk of PJI (14).

Cefazolin produces its antibacterial effect by inhibiting penicillin-binding proteins (PBPs), which are essential for the crosslinking of peptidoglycan in the bacterial cell wall which is necessary for the structural integrity of the bacterial cell wall (15). Additionally, cefazolin may inhibit the activity of gamma chain receptor-dependent cytokines, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, resulting in an anti-inflammatory effect (16). Its antimicrobial spectrum includes Gram-positive bacteria such as *Streptococcus*, *Staphylococcus*, and *Enterococcus*, as well as Gram-negative bacteria like *Haemophilus*, *Klebsiella*, *Escherichia*, *Proteus*, *Pseudomonas*, *Serratia*, and *Enterobacter* (17).

Cefazolin's pharmacological properties and broad-spectrum coverage include the most common pathogens associated with periprosthetic joint infections, making it an excellent choice as the primary prophylactic agent. Wyles and colleagues investigated the efficacy of cefazolin compared to alternative agents used in cases of cefazolin allergy. Their study revealed that cefazolin use reduced the risk of PJI by 32% compared to alternatives. Furthermore, they found cefazolin to be safe for patients with a reported penicillin allergy (18). Chaudry and colleagues investigated the cross-reactivity between penicillin and cephalosporins, highlighting the critical role of the R1 side chain in allergic reactions. Their analysis demonstrated that cefazolin has a unique R1 side chain distinct from that found in most penicillins, significantly reducing the risk of cross-reactivity (19). Additionally, cefazolin exhibits an acceptable safety profile, boasting a low risk of hypersensitivity and allergic reactions, with infrequent adverse effects. While rare, cases of *Clostridium difficile* infection and oral candidiasis, nephrotoxicity, and neurological hyperactivity with risk of seizures have been reported following cefazolin administration (20).

Cefuroxime is another single-agent antibiotic approved for prophylaxis prior to total joint arthroplasty. As a second-generation cephalosporin, cefuroxime has less activity against Gram-positive cocci compared to first-generation cephalosporins like cefazolin but offers enhanced activity against Gram-negative bacilli. The recommended dosage is a standard 1500 mg administered within one hour before surgery, which is weight independent. A meta-analysis conducted by Ahmed and colleagues compared the efficacy of cefazolin and cefuroxime in preventing surgical site infections and found no significant differences between the two agents. The authors concluded that both antibiotics are equally effective in preventing surgical site infections; however, due to its cost-effectiveness, cefazolin was recommended as the first-choice prophylactic agent (21).

Vancomycin is a glycopeptide antibiotic which functions by binding to the terminal D-alanyl-D-alanine residues of NAM/NAG-peptides, thereby preventing their incorporation into the peptidoglycan matrix and inhibiting bacterial cell wall synthesis. Additionally, vancomycin disrupts

bacterial cell membrane permeability and interferes with RNA synthesis (22). Its antimicrobial activity is limited to Gram-positive bacteria, with no effect on Gram-negative organisms, mycobacteria, or fungi. The recommended dosage of vancomycin for perioperative prophylaxis is weight-based, at 15 mg/kg, and should be administered as a slow infusion within two hours before surgery. Kheir and colleagues evaluated the efficacy and safety of vancomycin as a single agent for perioperative prophylaxis in total joint arthroplasty. Their analysis found vancomycin to be less effective than cefazolin in preventing surgical site infections (2% vs 1% of PJI respectively). They concluded that vancomycin not only has a less favorable bacterial coverage profile but is often underdosed (in 64% of cases) or administered at an inappropriate time (in 72% of cases). These factors frequently result in failure to achieve adequate therapeutic concentrations thus compromising its effectiveness (23). Additionally, vancomycin has a narrow therapeutic index, increasing the risk of systemic complications such as nephrotoxicity, red man syndrome, phlebitis, neutropenia, thrombocytopenia, and other allergic reactions. The authors recommend restricting the use of vancomycin as a single prophylactic agent. For these reasons, the use of intravenous vancomycin is primarily reserved for cases of verified anaphylaxis to cefazolin.

Dual Antibiotic Prophylaxis

The combination of two perioperative antibiotics has been studied to determine whether they provide greater efficacy in reducing the incidence of periprosthetic joint infections compared to single-agent prophylaxis. Multi-drug protocols typically include combinations of cephalosporins, aminoglycosides, and glycopeptides. Peel and colleagues conducted a multicenter, randomized, placebo-controlled trial to evaluate the efficacy of double antibiotic prophylaxis with cefazolin and vancomycin in patients without MRSA colonization. They concluded that adding vancomycin to antibiotic prophylaxis with cefazolin was not superior to placebo in preventing surgical site infections (24). However, adding vancomycin to the prophylactic regimen may be beneficial for patients colonized with MRSA, or at high risk for MRSA infection, such as healthcare workers, institutionalized patients, and those treated in centers with a high prevalence of MRSA infections (25, 26, 27).

Another commonly used antibiotic in dual prophylaxis are aminoglycosides. Ashkenazi and colleagues conducted a retrospective cohort study of patients undergoing primary total knee arthroplasty (TKA) to analyze the effect of gentamicin in combination with cefazolin. The study showed a slight, yet statistically insignificant, reduction in surgical site infections in the gentamicin group (0.86% vs. 1.3% in the control group, $p = 0.43$), without significant increase in gentamicin associated complications. The authors' final recommendation was against the routine use of a single dose of gentamicin in combination with routine cefazolin for dual antibiotic prophylaxis (28).

Aminoglycosides may still be useful in specific situations, such as patients at high risk of gram-negative infections, especially those in institutions with a high prevalence of such infections. Additionally, they may be considered for patients with anaphylactic reaction to cefazolin who receive vancomycin. Adding gentamicin or tobramycin in such scenarios can broaden and extend bacterial coverage. There are concerns about the cumulative side effects with the concurrent administration of glycopeptides and aminoglycosides, particularly nephrotoxicity and ototoxicity (29,30). Further research is required before aminoglycosides can be recommended for use in dual prophylaxis.

Local Perioperative Antibiotic Delivery Systems

Intraosseous Regional Antibiotics

Local antibiotic delivery systems offer the advantage of delivering high concentrations of antibiotics directly to the surgical field, maximizing antimicrobial efficacy while minimizing systemic side effects. One emerging technique in this regard involves the intramedullary injection of antibiotics at the surgical site, known as intraosseous regional antibiotics (IORA) (31,32). This technique achieves significantly higher tissue concentrations of antibiotics compared to systemic intravenous routes,

despite requiring smaller dosages. This not only reduces the potential for antibiotic-related side effects but also shows promise in lowering postoperative infection rates (33-42).

IORA offers additional benefits, including shorter infusion times and reduced susceptibility to variations in patient body weight (31-35, 37-41). It is particularly advantageous for patients requiring vancomycin, as it eliminates the need for prolonged infusion times and minimizes systemic effects such as nephrotoxicity and red man syndrome. Additionally, IORA has demonstrated improved tissue concentrations when used with cefazolin (38, 41).

The efficacy of IORA remains significant even when performed without a tourniquet for total hip arthroplasty (THA) or with limited tourniquet use for total knee arthroplasty (TKA) (34,35). A recent meta-analysis of data from four randomized controlled trials performed by Miltenberg et al, revealed that tissue concentrations of antibiotics with IORA in TKA are, on average, ten times higher than those achieved with IV infusion, along with significantly lower postoperative rates of periprosthetic joint infection (PJI) (43).

Topical Vancomycin Powder

Another widely used antibiotic delivery system is the direct application of antibiotic powder into the surgical field, with vancomycin powder (VP) being the most commonly used agent. Local application of VP achieves concentrations up to ten times the therapeutic levels, lasting for at least 24 hours post-wound closure, with minimal systemic absorption (44). VP has shown potential to reduce rates of postoperative deep joint infections (45-53). Some studies, however, have raised concerns about increased rates of wound complications associated with VP use (52-54). A 2023 randomized controlled trial (RCT) involving 165 patients (80 receiving VP and 85 controls) was stopped early after one-year preliminary data demonstrated a higher incidence of periprosthetic joint infections (PJI) in the VP group (n = 3) compared to the control group (n = 0). Additionally, eight patients in the VP group experienced postoperative complications such as myocardial infarction, pulmonary embolism, or anemia requiring transfusion, compared to only two patients in the control group (55). A randomized controlled trial by Mulpur et al., involving 1,022 patients, found no significant difference in periprosthetic joint infection (PJI) rates at 12 months (p = 0.264). However, the study did report a significantly higher rate of postoperative wound complications in the vancomycin powder (VP) group (13.2% vs. 7.56%), with an odds ratio of 1.64 for minor wound complications (56). Given the methodological limitations and heterogeneity of many retrospective studies—along with the lack of compelling results from more rigorous RCTs—a 2023 editorial in *The Bone & Joint Journal* concluded that “the evidence is not strong enough to recommend the use of vancomycin powder.” (57)

Antibiotic-Laden Materials

Antibiotic-laden bone cement (ALBC) is another vehicle for local antibiotic delivery that is often used in the setting of existing prosthetic joint infection and has been evaluated for use in primary total knee arthroplasty (58). Numerous large systematic reviews and RCTs alike suggest that ALBC is not associated with decreased rates of post-operative infection (58-60). The technique has been associated with significantly higher procedure costs without statistically significant reduction in infection rates (61). Calcium phosphate antibiotic beads are an alternative local antibiotic delivery system that has shown success in reducing both planktonic and biofilm forms of bacteria in-vitro (62). Vancomycin and tobramycin are the most commonly used antibiotics with this delivery vehicle. Lachica and coauthors conducted a randomized controlled trial evaluating the effectiveness of vancomycin-loaded calcium sulfate in reducing the risk of periprosthetic joint infection (PJI) in patients with non-modifiable risk factors. Their study demonstrated a significant reduction in three-month postoperative PJI rates compared to patients receiving intravenous antibiotics alone (63). However, the use of calcium sulfate beads has been associated with specific complications, including wound drainage, hypercalcemia, and potential abrasion of the implants' bearing surface (64,65). Due to these concerns, their use during primary total joint arthroplasty has not gained widespread acceptance and is primarily reserved for the management and treatment of PJI (65).

Antibiotic Irrigation Solutions

Antibiotic irrigation solutions were evaluated in the context of primary total joint arthroplasty. Goswami and coauthors reported the inferiority of polymyxin-bacitracin, vancomycin, and gentamicin solutions compared to povidone-iodine or chlorhexidine solutions in eradicating *Staphylococcus* and *Escherichia coli* in vitro. Chlorhexidine demonstrated a favorable antibacterial effect, but was also cytotoxic to fibroblasts. Povidone-iodine showed antibacterial efficacy without significant cytotoxicity (66). Similarly, Anglen and colleagues observed a lack of superiority of antibiotic irrigation solutions intraoperatively. In their randomized trial comparing bacitracin solution to castile soap solution for irrigation in open fracture cases, they found no significant differences in the rate of SSI and fracture healing complications between the two agents (67). In a meta-analysis of randomized controlled trials evaluating the efficacy of different irrigation solutions for preventing surgical site infections in general surgery, de Jonge and colleagues reported the superiority of povidone-iodine solution over antibiotic solutions (68).

Dilute Betadine Lavage

Unlike other antibiotic solutions, there has been growing evidence that dilute betadine lavage (DBL) is associated with decreased rates of postoperative infection in primary total joint arthroplasty (69–72). A 2018 analysis found DBL to be highly cost effective as a infection prophylactic measure in primary total joint arthroplasty (73). However, other studies have raised skepticism. A large retrospective cohort study by Hernandez et al. analyzed the use of dilute betadine lavage (DBL) during primary total hip and knee arthroplasty (THA and TKA) compared to procedures without DBL. The study found no significant reduction in infection-related reoperations associated with betadine use(74).

Other Techniques

Antibiotic-laden sponges have gained interest with mixed evidence in other surgical fields, however, research on their application to hip and knee arthroplasty is limited without significant evidence to support an association with reduced infection rates despite some concerns for technique-related complications (75, 76).

Intra-articular injection of antibiotic solution, usually vancomycin with or without tobramycin in normal saline injected after fascial closure, has been shown to have high intra-articular antibiotic concentrations up to 48 hours post-operatively without toxic systemic levels, but data regarding clinical implications and effectiveness is limited (77-80).

Extended Postoperative Antibiotic Prophylaxis

The use of extended postoperative antibiotics remains a topic of debate. While the American Association of Hip and Knee Surgeons (AAHKS) recommends administering parenteral antibiotics during the first 24 hours postoperatively, the latest CDC guidelines do not support their use after wound closure (81, 82). A recent meta-analysis of 14 studies by Siddiqi et al found no difference in PJI rates between patients who received a single preoperative antibiotic dose and those who underwent extended parenteral postoperative prophylaxis. However, the authors noted that many of these studies were underpowered and potentially biased (83).

Several studies have suggested that extended oral postoperative antibiotic prophylaxis may reduce the risk of PJI, particularly in high-risk patients. Those considered high risk include individuals with a high body mass index (BMI 35 kg/m² or higher), active smoking status, diabetes, autoimmune disease, chronic kidney disease, or colonization with methicillin-sensitive *Staphylococcus aureus* (MSSA) or methicillin-resistant *Staphylococcus aureus* (MRSA). In this population, the use of extended oral antibiotic prophylaxis with cefadroxil reduced the risk of SSI at 90 days postoperatively by four times compared to those who did not receive postoperative antibiotics (84). Additionally, a retrospective study by Khair et al. found a statistically significant

reduction in 1-year PJI rates among patients who received extended oral antibiotics for seven days postoperatively (85).

Despite these findings, a recent study by Flynn and colleagues reported no statistically significant difference in 1-year PJI rates between high-risk patients who received extended oral antibiotic prophylaxis and those who received only the standard perioperative antibiotic prophylaxis with intravenous Ancef and Vancomycin (86). Further large-scale, prospective, randomized trials are needed to elucidate whether extended oral antibiotic prophylaxis provides a meaningful benefit for high-risk patients.

DISCUSSION

Periprosthetic joint infection remains a significant concern in total joint arthroplasty, with multiple established risk factors. These risks can be divided into patient-related and surgery-related factors. Patient-related risk factors include obesity (BMI 35 kg/m² or higher), diabetes, malnutrition, anemia, smoking, *Staphylococcus aureus* colonization, vitamin D deficiency, active urinary tract infections, poor dental hygiene, and chronic renal, cardiac, autoimmune or inflammatory diseases. Surgery-related factors include perioperative sterility, surgical time, type of anesthesia, surgical site preparation, perioperative antibiotic prophylaxis, surgical technique, blood preservation, wound management, and pain control. Since many surgical risk factors are modifiable, implementing strategies to reduce infection risk is critical. Among these, prophylactic antibiotic use plays a key role in minimizing the likelihood of PJI. Current CDC guidelines support the administration of a single preoperative dose of an antibiotic, preferably a first-generation cephalosporin, within one hour of incision as a key recommendation in preventing PJIs. Intraosseous antibiotic prophylaxis has emerged as a promising method in total knee arthroplasty, particularly when a tourniquet is used. This technique enables timely antibiotic administration before surgery, achieving high tissue concentrations while minimizing systemic exposure. It is especially beneficial when dual antibiotic prophylaxis is utilized with vancomycin, as intraosseous delivery ensures effective tissue penetration without the need for strict dosing protocols. Additional Level 1 evidence is needed to evaluate the safety and efficacy of intraosseous prophylaxis in total hip arthroplasty. Extended postoperative antibiotic prophylaxis remains variable and further higher-level studies are warranted to elucidate whether these protocols are effective in reducing the rate of PJIs.

Based on current available literature, we recommend the routine use of a single preoperative dose of cefazolin based on the body weight, dual antibiotic prophylaxis with Vancomycin for patients with MRSA colonization, health care workers or institutionalized patients. For patients considered to be at high risk for PJI, a 7 day extended postoperative course of antibiotics should be considered.

Other antibiotic protocols and routes of administration remain controversial and require further research to establish their effectiveness.

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