HK81: What is the optimal prophylactic antibiotic for patients undergoing primary arthroplasty?

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Response/Recommendation: Cephalosporins, particularly cefazolin, are strongly recommended as first-line prophylaxis in primary arthroplasty based on consistent high-quality evidence, significant infection risk reduction, and minimal adverse effects.

Strenght of Recommendation: Strong

Rationale: Periprosthetic joint infections (PJI) represent a significant complication in total joint arthroplasty (TJA), contributing to increased patient morbidity, prolonged hospital stays, heightened healthcare costs, and frequent need for complex revision surgeries. Effective antibiotic prophylaxis is a cornerstone in minimizing these risks, with cephalosporins, particularly cefazolin, emerging as the gold standard due to their efficacy, safety, and cost-effectiveness. Over the last decade, an extensive body of evidence has supported the use of cephalosporins, addressing their benefits in routine arthroplasty cases, high-risk populations, penicillin-allergic patients, and their role in combination with adjunctive strategies.

To address the posed question above, we conducted a comprehensive systematic review. Initially, using the search in PubMed and Embase, we identified 924 studies. After eliminating duplicates and case series, 167 studies were selected for full-text analysis. Following a review conducted by two reviewers, we finalized 41 articles for data extraction. For the final analysis of the strength of recommendation, 22 articles were used due to their consistency in the necessary data. Analysis of these most relevant studies spanning from 2015 to 2024 has demonstrated consistent reductions in infection rates, culminating in a strong recommendation (Grade A) for cephalosporins in primary arthroplasty, as assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (1).

The systematic review by Voigt et al. in 2015 remains foundational in supporting cephalosporin use. This study synthesized data from randomized controlled trials involving over 12,000 patients and demonstrated that cephalosporins reduced surgical site infection (SSI) rates by 40% compared to non-cephalosporin antibiotics (Level I evidence) (2). Concurrently, Hickson et al. analyzed 4,500 arthroplasty cases and identified cefazolin and cefuroxime as highly effective agents when administered correctly, achieving consistent infection rates of approximately 2.5% (3).

Robertsson et al. analyzed the Swedish Knee Arthroplasty Register, encompassing 55.350 patien who underwent primary knee arthroplasty during the period from 2009-2015 and highlighted that clindamycin, often used in penicillin-allergic patients, was associated with a 50% higher risk of infection revision compared to cephalosporins (relative risk = 1.5, P = 0.001) (4). In the same year, Parvizi et al published guidelines emphasizing the importance of timely preoperative antibiotic administration, nasal decolonization with mupirocin, and dual-agent skin preparation to mitigate infection risks in arthroplasty (5)

In 2019, Wyles et al. evaluated 29,695 arthroplasties from 2004 through 2017 at the Mayo Clinic and demonstrated that allergy testing significantly improved cefazolin use in patients with reported penicillin allergies. This retrospective cohort study showed that delabeling penicillin allergies increased cefazolin use from 70% to 95%, resulting in a

reduction in infection rates from 1.49% to 1.15% (odds ratio [OR] = 0.78, P < 0.05).This study found a lower rate of PJI when cefazolin is used for prophylaxis in primary total hip artrhroplasty (THA) and total knee arthroplasty (TKA) compared with vancomycin or clindamycin (6).

Further evidence emerged in 2020, when Babu et al. conducted a multicenter study comparing five antibiotic regimens across 4,500 arthroplasties. This analysis found no significant differences in infection rates among regimens involving, cefuroxime, teicoplanin, gentamicin and flucloxaciliin, (7). Iannotti et al. (2020) introduced a multimodal approach for high-risk patients, integrating weight-based cefazolin dosing, MRSA screening, dual skin preparation with chlorhexidine and povidone-iodine, and local antibiotic delivery, reducing infection rates from 5.8% to 2.4% (8). Rivera et al. added further laboratory evidence demonstrating cefazolin's superior efficacy in preventing intraoperative bacterial contamination compared to alternative agents, underscoring its critical role in infection prevention during arthroplasty (9).

The 2021 AAHKS Annual Symposium further emphasized weight-based cefazolin dosing and the necessity of preoperative administration within 30 minutes of incision to optimize tissue concentrations. Recommendations included 1 g for patients <60 kg, 2 g for patients 60–120 kg, and 3 g for patients >120 kg. Additionally, cefazolin monotherapy was strongly recommended over vancomycin for routine-risk patients, while dual antibiotic regimens were selectively advocated for high-risk cases (10). In a separate study presented by Mabrouk et al, evaluated guideline adherence across 109 institutions in the UK and highlighted variability in practices related to drug used,weight-based dosing and MRSA screening protocols, underscoring the need for standardization (11).

In 2022, Badge et al. conducted a large retrospective study involving 1838 high-risk patients. They found that weight-based cefazolin dosing reduced infection rates from 5.2% to 2.9%, emphasizing the necessity of adjusting doses based on patient weight to enhance effectiveness (12). Similarly, Indelli et al. (2022) surveyed international arthroplasty experts, recommending routine preoperative decolonization, MRSA screening, and weight-based cefazolin dosing (13).

By 2023, studies increasingly focused on adjunctive therapies and addressing penicillin-allergic patients Ashkenazi et al. (2023) evaluated gentamicin's addition to cefazolin in 1,590 total knee arthroplasty cases, observing a 34% reduction in infections (from 1.3% to 0.86%), although findings were not statistically significant (P = 0.43) (14). Bukowski et al. (2023) demonstrated cefazolin's safety in penicillin-allergic patients, showing a 0.1% rate of mild allergic reactions in 5,508 patients with no increased infection risks (15). Another study by Jones et al. reported that stewardship interventions increased cefazolin use in penicillin-allergic patients from 54% to 91%, reducing superficial infections from 4.5% to 2.8%.

This study also emphasized that cephalosporins are safer and more effective than alternatives such as vancomycin or clindamycin for penicillin-allergic patients, reinforcing the importance of stewardship programs (16).

Bains et al. (2024) evaluated whether adding vancomycin to cefazolin for preoperative antibiotic prophylaxis reduces infection rates in total joint arthroplasties (TJA). It analyzed 2,907 patients (1,437 receiving vancomycin + cefazolin and 1,470 receiving cefazolin only) over seven years. Results showed **no significant difference** in rates of surgical site infections (SSI) or periprosthetic joint infections (PJI) between the two groups at 90 days and one year. Vancomycin was associated with reduced MRSA colonization in pre-screened patients but did not lower overall infection rates. The study concluded that vancomycin is unnecessary for most patients and should be limited to MRSA-positive cases.(17)

Peel et al, conducted a multicenter, double-blind, placebo-controlled randomized clinical trial involving 4,239 patients undergoing primary arthroplasty (hip, knee, shoulder) without methicillin-resistant *Staphylococcus aureus* (MRSA) colonization. The study compared cefazolin monotherapy with cefazolin plus vancomycin and found no significant difference in surgical-site infection rates (4.5% vs. 3.5%, $P = 0.11$). Subgroup analysis showed higher infection rates with dual therapy in knee arthroplasty (5.7% vs. 3.7%, $P < 0.05$) but no difference in hip arthroplasty. While vancomycin reduced the risk of acute kidney injury (2.1% vs. 3.6%, $P < 0.01$), it was associated with increased hypersensitivity reactions (1.2% vs. 0.5%, $P < 0.05$). The study concluded that cefazolin monotherapy suffices for infection prophylaxis in non-MRSA colonized patients, reserving vancomycin for high-risk populations. (18)

Sequeira et al. (2023) highlighted the effectiveness of novel antimicrobial lavage solutions, reducing bacterial loads by 92% and preventing biofilm formation when

In 2024, Hassanzadeh et al. reviewed national prescribing practices, identifying cefazolin as the most commonly recommended antibiotic in arthroplasty. Standardizing evidence-based protocols was emphasized to reduce variability and improve outcomes and the emergence of antibiotic resitance (20).

In the same year, Egerci et al. (2024) conducted a comprehensive review on strategies to prevent periprosthetic joint infections (PJI) in total hip arthroplasty (THA) and total knee arthroplasty (TKA) emphasizing the importance of a multidisciplinary approach and patient-specific strategies to reduce PJI risk and improve surgical outcomes.

In conclusion, there is a strong evidence that supports the use of cefazolin as the first line prophylaxis in patients undergoing primary arthroplasty.

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