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Bacterial Profiles and Empiric Antibiotic Therapy in Prosthetic Joint Infection: A Systematic Literature Review

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ABSTRACT

Introduction: Prosthetic joint infection (PJI) is a serious complication of joint arthroplasty that requires appropriate antimicrobial therapy. This systematic literature review aimed to identify the predominant bacterial pathogens associated with PJI and summarize empiric antibiotic regimens used in its management.
Methods: A literature search was conducted using Google Scholar for studies published between 2019 and 2023. Studies involving patients with PJI, microbiological culture findings, and empiric antibiotic therapy were included. Data were synthesized descriptively.
Results: Five retrospective studies involving 555 patients met the eligibility criteria. *Staphylococcus aureus* was the most consistently reported causative pathogen, followed by coagulase-negative staphylococci and several Gram-negative organisms. Empiric regimens varied considerably and included vancomycin, fluoroquinolones, cefazolin, flucloxacillin, amoxicillin/clavulanate, and combination therapies. Vancomycin-based combinations with imipenem or ciprofloxacin provided broad antimicrobial coverage in several studies. However, the optimal regimen differed according to bacterial distribution, resistance patterns, and clinical setting.
Conclusion: *Staphylococcus aureus* was the predominant pathogen identified in PJI. Empiric antibiotic therapy should provide appropriate staphylococcal coverage while considering additional Gram-negative coverage when indicated. Treatment should be guided by local antimicrobial susceptibility patterns and subsequently adjusted according to culture and sensitivity results.

Keywords: antibacterial agents; prosthesis-related infections; *Staphylococcus aureus*; vancomycin.

INTRODUCTION

Prosthetic joint infection (PJI) is a serious complication occurring in approximately 1–2% of primary joint arthroplasties and is associated with substantial morbidity and complex treatment requirements. As life expectancy increases and older populations maintain greater expectations for mobility and functional independence, the number of joint arthroplasty procedures continues to rise. Consequently, the overall burden of PJI is also expected to increase.[1] PJI may be

classified according to the time of onset after surgery as acute (<3 months), subacute (3–12 months), or chronic (>1 year). Acute PJI is frequently encountered and is commonly managed using debridement, antibiotics, and implant retention (DAIR), although reported success rates vary considerably, ranging from 23% to 100%.[2] Management of PJI is challenging and may require repeated surgical procedures combined with prolonged antimicrobial therapy. Accurate identification of the causative microorganism and its antimicrobial susceptibility profile is therefore essential for selecting appropriate definitive treatment. Failure to adequately identify and control the infection may result in persistent infection, repeated surgery, functional impairment, and a substantial reduction in quality of life.[1]

In addition to increasing treatment duration and healthcare costs, PJI can substantially affect patient outcomes and quality of life. Rational antimicrobial therapy is therefore essential. Inappropriate antibiotic use may result in adverse effects and contribute to the development of antimicrobial resistance. However, empiric antibiotic practices in PJI remain variable, particularly with regard to antibiotic selection, dosage, timing, and duration of administration.[3] Because empiric therapy is often initiated before microbiological culture and susceptibility results are available, knowledge of the predominant causative organisms is important for selecting appropriate initial antimicrobial coverage. Therefore, this systematic literature review aimed to characterize the bacterial pathogens commonly associated with PJI, summarize the empiric antibiotic regimens used in its management, and evaluate the relationship between the reported bacterial profiles and the antimicrobial coverage provided by empiric therapy. The findings are expected to provide evidence that may support the selection of appropriate empiric antimicrobial treatment while awaiting definitive microbiological results.

METHODS

Search strategy and data sources

A systematic literature search was conducted using Google Scholar to identify studies evaluating bacterial pathogens and empiric antibiotic therapy in PJI. The search covered articles published between 2019 and 2023 and used combinations of the keywords "antibiotic," "therapy," "prosthetic joint infection," and "hip." Relevant articles were subsequently screened according to predefined eligibility criteria.

Review question and PICO framework

The review question was formulated using the Population, Intervention, Comparison, and Outcome (PICO) framework. The population comprised patients with PJI; the intervention of interest was empiric antibiotic therapy; comparisons included different empiric antibiotic regimens and their antimicrobial coverage against the identified pathogens; and the outcomes included bacterial profiles, antimicrobial susceptibility or coverage, and reported treatment outcomes. The PICO framework is summarized in Table 1.

Table 1. PICO Framework of the Systematic Literature Review

PICO Component	Description
P – Population	Patients with PJI
I – Intervention	Empiric antibiotic therapy for PJI
C – Comparison	Different empiric antibiotic regimens and their coverage against identified causative pathogens
O – Outcome	Bacterial profiles, antimicrobial coverage or susceptibility, and reported treatment outcomes

Eligibility criteria

Studies were eligible if they included patients with PJI, evaluated empiric

antibiotic therapy, reported microbiological culture findings and corresponding antimicrobial coverage or susceptibility, and/or reported outcomes following empiric treatment. Articles published in English or Indonesian were considered eligible. Case reports, studies involving patients who had previously undergone implant revision, and studies involving repeated treatment within a short interval were excluded.

Study selection

Records identified through the literature search were screened according to the predefined eligibility criteria. Potentially relevant articles underwent further eligibility assessment, and studies fulfilling all criteria were included in the final review. Figure 1 illustrates the literature search and study selection process.

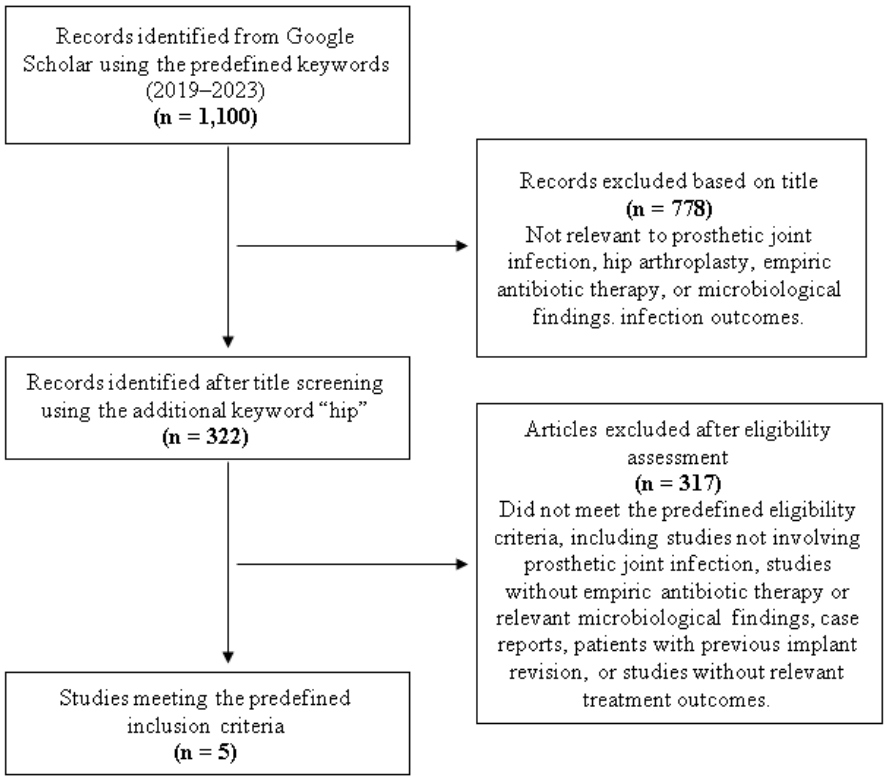


Figure 1. Flow diagram of the literature search and study selection process

Data synthesis

Data were extracted from the included studies and synthesized descriptively. Extracted variables included study design, sample size, bacterial isolates, empiric antibiotic regimens, antimicrobial coverage or susceptibility, and reported treatment outcomes. The findings were compared to identify patterns in the causative organisms and the empiric antimicrobial strategies used for PJI.

RESULTS

Five retrospective studies involving a total of 555 patients with PJI met the predefined eligibility criteria. The characteristics and main findings of the included studies are summarized in Table 2. *Staphylococcus aureus* (*S. aureus*) was the most frequently reported pathogen across the included studies, followed by coagulase-negative staphylococci and various Gram-negative and streptococcal organisms. Empiric antimicrobial strategies varied considerably and included vancomycin-based combinations, cefazolin, flucloxacillin, amoxicillin/clavulanate, and other combination regimens. Several studies reported broader antimicrobial coverage with combination therapy, particularly

vancomycin combined with an agent providing additional Gram-negative coverage.

Table 2. Characteristics, bacterial profiles, and empiric antibiotic findings

Author, Year	Sample Size	Study Design	Main Bacterial Findings	Empiric Antibiotic Findings
Scholten et al., 2021[2]	111	Retrospective cohort study	The most frequently identified pathogens were *S. aureus*, coagulase-negative staphylococci, and Enterobacterales. *S. aureus* was the predominant pathogen.	Vancomycin-based therapy provided broad coverage despite the absence of MRSA in the isolates. Vancomycin plus ciprofloxacin or a third-generation cephalosporin achieved high antimicrobial coverage, with vancomycin plus ciprofloxacin providing the broadest coverage in this study.
Ma et al., 2023[4]	76	Retrospective study	The most frequently isolated pathogens were *S. aureus*, coagulase-negative staphylococci, and Pseudomonas/Enterobacter. *S. aureus* was the predominant pathogen.	Imipenem plus vancomycin provided the broadest antimicrobial coverage (88.2%), followed by ciprofloxacin plus vancomycin and piperacillin/tazobactam plus vancomycin (85.3%).
Auñón et al., 2022[5]	45	Retrospective study	PJI was caused by *S. aureus*.	A regimen of daptomycin plus high-dose cloxacillin for 5 days followed by levofloxacin plus rifampicin was associated with better outcomes than the previous antibiotic regimen in patients with acute *S. aureus* PJI treated with DAIR.
Kim et al., 2022[6]	232	Retrospective study	The predominant pathogens were *S. aureus*, coagulase-negative staphylococci, and Streptococcus spp., with *S. aureus* being the most frequently identified organism.	Vancomycin provided broader coverage than flucloxacillin for early PJI. Addition of Gram-negative coverage resulted in >90% antimicrobial coverage. For late PJI, cefazolin or flucloxacillin provided adequate Gram-positive coverage while awaiting culture and susceptibility results.
Van Erp et al., 2019[7]	91	Retrospective study	The predominant pathogens were *S. aureus*, coagulase-negative staphylococci, and non-group A/B hemolytic streptococci. *S. aureus* was the most frequently identified pathogen.	Amoxicillin/clavulanate, cefazolin, and flucloxacillin were evaluated as empiric treatment options. Cefazolin and amoxicillin/clavulanate provided greater antimicrobial susceptibility coverage than flucloxacillin.

DISCUSSION

Bacterial profile in PJI

The findings of this systematic literature review indicate that *S. aureus* remains an important pathogen in PJI. Although the microbiological profiles varied among the included studies, staphylococcal species were consistently prominent, supporting the importance of adequate Gram-positive coverage when initiating empiric antimicrobial therapy. [2,4-7] *S. aureus* is a Gram-positive organism that commonly colonizes the skin and mucosal surfaces but is also an important cause of skin and soft-tissue infection, osteomyelitis, surgical site infection, bloodstream infection, and other

invasive infections. Its pathogenicity is related to several virulence factors and enzymes that facilitate tissue invasion and persistence. The clinical relevance of *S. aureus* in PJI is further complicated by methicillin-resistant *S. aureus* (MRSA), in which the mecA gene encodes an altered penicillin-binding protein with reduced affinity for methicillin and other β-lactam antibiotics.[8]

The predominance of staphylococci observed in the included studies therefore has important implications for empiric antibiotic selection. Empiric treatment should provide sufficient initial coverage against likely Gram-positive pathogens while also considering the possibility of resistant organisms. However, because Gram-negative organisms were also identified in several studies, particularly in early or polymicrobial infections, Gram-positive coverage alone may not always be sufficient.

Empiric antibiotic therapy in PJI

Empiric antibiotic therapy is initiated when infection is suspected but the causative microorganism and antimicrobial susceptibility profile have not yet been established. Its primary purpose is to suppress or eradicate the most likely pathogens while microbiological results are pending. Once culture and susceptibility results become available, the regimen should be adjusted to pathogen-directed therapy.[9] Management of acute PJI generally requires both surgical and antimicrobial treatment. Debridement, antibiotics, and implant retention (DAIR) is commonly used in appropriately selected acute cases.[2] Because the bacterial profile is initially uncertain, adequate empiric antimicrobial coverage is particularly important during the early treatment phase. Nevertheless, excessively broad or prolonged antimicrobial exposure should be avoided because it may increase toxicity and promote antimicrobial resistance.[10]

The included studies demonstrate that there is no single empiric regimen that can be universally applied to all patients with PJI. Instead, antimicrobial selection should reflect the expected bacterial spectrum and local susceptibility patterns. Vancomycin was frequently incorporated into broad empiric strategies because of its activity against Gram-positive organisms, particularly MRSA. Vancomycin inhibits bacterial cell-wall synthesis and has strong bactericidal activity against susceptible staphylococci; however, it does not provide activity against Gram-negative organisms. [9,11]

This limitation provides a rationale for combining vancomycin with an antimicrobial agent that provides additional Gram-negative coverage in selected patients. A study shows the combination of imipenem and vancomycin provided the broadest coverage among the evaluated regimens.[4] Similarly, Scholten reported high coverage with vancomycin combined with ciprofloxacin or a third-generation cephalosporin.[2] These findings suggest that combination therapy may be particularly relevant when the causative organism is unknown and both resistant Gram-positive and Gram-negative pathogens need to be considered. Imipenem provides broad antimicrobial activity against many Gram-positive, Gram-negative, and anaerobic organisms and achieves good penetration into body tissues and fluids.[11] Its combination with vancomycin can therefore provide complementary antimicrobial coverage. However, broader coverage should not automatically be interpreted as superior treatment for every patient. The potential benefits should be weighed against adverse effects, antimicrobial resistance, renal function, and the likelihood of particular pathogens.

Role of fluoroquinolones and biofilm activity

Biofilm formation is particularly important in PJI because microorganisms adhering to prosthetic surfaces may become more difficult to eradicate and less susceptible to conventional antimicrobial therapy.

Antibiotic selection should therefore consider not only microbiological susceptibility but also activity against organisms within biofilms.

Fluoroquinolones, particularly ciprofloxacin, have demonstrated favorable in vitro activity against biofilms produced by several Gram-negative organisms. Their biofilm activity has been particularly described for Pseudomonas aeruginosa, although activity against organisms such as Escherichia coli has also been reported.[12] This characteristic may partly explain the use of ciprofloxacin-containing regimens in PJI when Gram-negative infection is suspected.

Nevertheless, fluoroquinolones should not be considered universally appropriate for all PJI. Their role depends on the causative organism, susceptibility profile, and individual patient factors. Their use as part of empiric combination therapy should therefore be reassessed once culture results become available.

Role of β-Lactam antibiotics

First-generation cephalosporins such as cefazolin provide strong activity against many Gram-positive cocci but do not provide reliable activity against MRSA and have only moderate coverage against selected Gram-negative organisms.[11] Cefazolin may therefore be an appropriate empiric option in settings where methicillin-susceptible staphylococci predominate and the prevalence of resistant organisms is low.

A study reported that vancomycin provided broader coverage for early PJI, whereas cefazolin or flucloxacillin could provide adequate Gram-positive coverage in later infections while awaiting definitive microbiological results.[6] Similarly, other study demonstrated that the appropriateness of commonly used empiric β-lactam regimens depended substantially on the susceptibility profile of the local PJI pathogens.[7] These findings emphasize that the selection of β-lactam therapy should be guided by local epidemiological and antimicrobial resistance patterns rather than by a universal regimen.

Combination Therapy

Combination antimicrobial therapy may be considered in circumstances where broader initial coverage is necessary, including severe infection, suspected polymicrobial infection, or uncertainty regarding the causative organism. Combining antimicrobial agents may result in additive or synergistic effects and may broaden the bacterial spectrum covered by initial treatment. However, combinations may also increase drug-related toxicity and antimicrobial selection pressure.

The findings of the included studies suggest that combination regimens may provide broader microbiological coverage than single-agent therapy in selected settings. In addition to vancomycin-based combinations, a study evaluated a treatment strategy incorporating daptomycin and cloxacillin followed by levofloxacin and rifampicin in acute *S. aureus* PJI managed with DAIR.[5] These findings support the potential role of combination strategies but should not be interpreted as evidence that one combination is universally preferable. The choice of therapy should remain individualized according to the identified or suspected microorganism, resistance profile, clinical severity, and surgical strategy.

Pharmacokinetic and pharmacodynamic considerations

Antibiotic selection for PJI should not be based solely on antimicrobial spectrum. Pharmacokinetic and pharmacodynamic (PK/PD) characteristics are also important because effective treatment requires adequate drug concentrations at the site of infection. Relevant parameters include peak serum concentration, minimum concentration, area under the concentration-time curve, time-dependent or concentration-dependent bactericidal activity, and persistent antimicrobial effects.[9,13]

Bone and joint infections are particularly challenging because antimicrobial agents must achieve sufficient penetration into bone, synovial tissues, and peri-prosthetic tissues. Several antimicrobial classes, including β-lactams, carbapenems, fluoroquinolones, vancomycin, linezolid, daptomycin, clindamycin, and trimethoprim/sulfamethoxazole, have demonstrated penetration into bone and joint tissues.[14] Therefore, the empiric agents identified in this review are generally consistent with the principle that antimicrobial therapy for PJI should combine an appropriate microbiological spectrum with adequate tissue penetration.

In clinical practice, the choice and dosage of empiric antibiotics should therefore consider local bacterial epidemiology and resistance patterns, the patient's clinical condition, antibiotic availability, tissue penetration, and the possibility of polymicrobial infection.[9] Once microbiological identification and susceptibility results are available, broad empiric therapy should be narrowed whenever possible.

Clinical Implications

Overall, the findings of this review support an empiric strategy that prioritizes adequate coverage against staphylococci while considering additional Gram-negative coverage when clinically indicated. The variability in antimicrobial recommendations among the included studies suggests that no single regimen can be considered optimal for all cases of PJI. Instead, empiric therapy should be selected according to the timing and severity of infection, local microbiological patterns, antimicrobial resistance, patient-specific factors, and the planned surgical strategy. Definitive treatment should subsequently be guided by culture and antimicrobial susceptibility results.

Limitations

This review has several limitations. Only five studies were included, and the evidence was predominantly derived from retrospective observational designs. Considerable heterogeneity was present in patient populations, timing and classification of PJI, microbiological profiles, antimicrobial regimens, and reported outcomes, limiting direct comparison among studies. Furthermore, the literature search was restricted to Google Scholar and studies published between 2019 and 2023, which may have resulted in relevant evidence being missed. Future studies using prospective designs and standardized definitions of PJI and treatment outcomes are needed to better determine the most appropriate empiric antimicrobial strategies.

CONCLUSION

This systematic literature review identified *S. aureus* as the most frequently reported pathogen in PJI. Empiric antibiotic regimens varied considerably and included vancomycin, fluoroquinolones, cefazolin, flucloxacillin, and amoxicillin/clavulanate. Vancomycin-based combinations, particularly with imipenem or ciprofloxacin, provided broader antimicrobial coverage in several studies. Overall, empiric therapy for PJI should be guided by the expected bacterial profile and local antimicrobial susceptibility patterns and subsequently adjusted according to culture and susceptibility results.

Declaration by Authors

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