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Antimicrobial Adverse Events in Periprosthetic Joint Infections: A Narrative Review of Incidence, Drug Class-Specific Toxicities, and Risk Factors

Periprostetik Eklem Enfeksiyonlarında Antimikrobiyal Yan Etkiler: Sıklık, İlaç Sınıfına Özgü Toksisiteler ve Risk Faktörleri Üzerine Anlatısal Bir İnceleme

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Abstract

Periprosthetic joint infection (PJI) is a severe complication of arthroplasty, frequently requiring prolonged antimicrobial therapy. Despite being essential for infection control, extended antibiotic exposure predisposes patients to adverse drug events (ADEs), which may compromise treatment efficacy and patient safety. This review aims to synthesize current evidence on the incidence, spectrum, and risk factors of antimicrobial-related ADEs in PJI, with an emphasis on drug class-specific toxicities and their therapeutic implications. A narrative literature search was conducted in PubMed, Embase, and the Cochrane Library from January 2010 to September 2025. Eligible studies included randomized trials, prospective and retrospective cohort studies, and systematic reviews evaluating ADEs associated with antimicrobial therapy for PJI. Data were extracted on incidence, severity, drug classes, treatment modifications, and identified risk factors. A narrative synthesis was performed because of methodological heterogeneity. Across the analyzed literature, the reported incidence of ADEs ranged from 7.8% to 46%, with approximately 7.8% to 20.4% classified as severe events. Vancomycin and piperacillin–tazobactam combinations showed the highest rates of nephrotoxicity, whereas rifampin and linezolid were commonly associated with hepatotoxicity and hematologic toxicity, respectively. Prolonged treatment duration, intravenous administration, advanced age, obesity, and comorbidities significantly increased the risk of ADEs. Emerging evidence suggests that oral step-down therapy and shorter antimicrobial regimens may provide comparable efficacy while offering improved safety profiles. Overall, antimicrobial-related ADEs are common and clinically significant in PJI management, often leading to treatment modification or discontinuation. Optimizing regimen selection, treatment duration, and monitoring, along with adopting standardized ADE reporting frameworks, remains essential to enhancing safety and therapeutic outcomes in PJI care.

Keywords: Periprosthetic joint infection, antimicrobial toxicity, adverse drug events, antimicrobial safety, risk factors



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Öz

Periprostetik eklem enfeksiyonu (PJI), sıklıkla uzun süreli antimikrobiyal tedavi gerektiren, artroplastinin ciddi bir komplikasyonudur. Enfeksiyon kontrolü için gerekli olmasına rağmen, uzun süreli antibiyotik maruziyeti hastaları, etkinliği ve hasta güvenliğini tehlikeye atabilecek advers ilaç olaylarına (ADE) yatkın hale getirir. Bu derleme, PJI'da antimikrobiyal ilaçlara bağlı ADE görülme sıklığı, yelpazesi ve risk faktörlerine ilişkin güncel kanıtları özetlemeyi amaçlamakta olup, ilaç sınıfına özgü toksik etkilere ve bunların terapötik sonuçlarına vurgu yapmaktadır. Ocak 2010 ile Eylül 2025 tarihleri arasında PubMed, Embase ve Cochrane Kütüphanesi'nde anlatsal bir literatür taraması yapılmıştır. PJI'ya yönelik antimikrobiyal tedaviyle ilişkili ADE'leri değerlendiren randomize çalışmalar, prospektif ve retrospektif kohortlar ve sistematik incelemeler çalışmaya dahil edilmiştir. İnsidans, şiddet, ilaç sınıfları, tedavi değişiklikleri ve belirlenen risk faktörlerine dair veriler çıkarılmıştır. Metodolojik heterojenlik nedeniyle anlatsal bir sentez yapılmıştır. Analiz edilen literatürde, bildirilen ADE'lerin insidansı %7,8 ile %46 arasında değişmekte olup, yaklaşık %7,8 ile %20,4'ü şiddetli olaylar olarak sınıflandırılmıştır. Vankomisin ve piperasilin-tazobaktam kombinasyonları en yüksek nefrotoksisite oranlarını gösterirken, rifampin ve linezolid sırasıyla hepatotoksisite ve hematolojik toksisite ile ilişkilendirilmiştir. Uzun süreli tedavi, intravenöz uygulama, ileri yaş, obezite ve eşlik eden hastalıklar ADE riskini önemli ölçüde artırmıştır. Ortaya çıkan kanıtlar, oral kademeli tedavi ve daha kısa antimikrobiyal rejimlerin, daha iyi güvenlik profilleri sunarken, karşılaştırılabilir etkinlik sağlayabileceğini göstermektedir. Antimikrobiyal ilişkili ADE'ler, PJI yönetiminde sık olarak ortaya çıkar ve klinik olarak önemlidir ve genellikle tedavi değişikliğine veya tedavinin sonlandırılmasına yol açar. Periprostetik eklem enfeksiyonu tedavisinde güvenliği ve terapötik sonuçları iyileştirmek için rejim seçiminin, süresinin ve takibinin optimize edilmesi ve standartlaştırılmış ADE raporlama çerçevelerinin benimsenmesi esastır.

Anahtar Kelimeler: Periprostetik eklem enfeksiyonu, antimikrobiyal toksisite, advers ilaç reaksiyonları, antimikrobiyal güvenlik, risk faktörleri

Introduction

Periprosthetic joint infection (PJI) is one of the most serious complications following arthroplasty, with reported incidence rates of approximately 1%-2% after primary arthroplasty and higher rates after revision procedures^[1,2]. These infections are associated with substantial morbidity, functional impairment, repeated hospitalizations, and increased healthcare expenditures^[3,4]. Management is complex and typically requires a multidisciplinary approach that combines surgical intervention with prolonged courses of pathogen-directed antimicrobial therapy^[5-7].

Antimicrobial therapy remains a cornerstone of PJI management, particularly the use of biofilm-active agents such as rifampin for staphylococcal infections^[8,9]. However, several characteristics specific to PJI management substantially increase the risk and clinical consequences of antimicrobial-associated adverse drug events (ADEs). Treatment duration is considerably longer than that for most infectious diseases, typically extending for 6-12 weeks and, among patients receiving suppressive antibiotic therapy (SAT), for months or even years^[5-7]. In addition, effective management of biofilm-associated infections often requires combination antimicrobial regimens, increasing the likelihood of drug-drug interactions and cumulative or overlapping toxicities^[2,10,11]. The use of agents with narrow therapeutic indices further increases the risk of treatment-related toxicity^[11]. These treatment-related factors are compounded by the demographic and clinical characteristics of patients with PJI, who are typically older and frequently have chronic kidney disease, obesity, and polypharmacy, all of which independently increase susceptibility to antimicrobial toxicity^[1,10,12]. Collectively, these disease- and treatment-specific characteristics distinguish

antimicrobial-related ADEs in PJI from the broader spectrum of antimicrobial toxicities and support their recognition as a distinct clinical challenge.

Class-specific toxicities are well established, including vancomycin-associated nephrotoxicity^[9], rifampin-related hepatotoxicity and drug-drug interactions^[13], linezolid-induced myelosuppression and neuropathy^[14], and *Clostridioides difficile* infection associated with broad-spectrum agents^[15]. Such toxicities can compromise patient safety and necessitate antimicrobial treatment modification or discontinuation, potentially jeopardizing infection control^[4]. Increasing evidence from prospective and retrospective studies has underscored the clinical significance of antimicrobial-associated ADEs in PJI. Prolonged antibiotic use beyond 1 year does not confer additional benefit but increases the risk of ADEs^[16]. Similarly, the choice between intravenous therapy and highly bioavailable oral agents is often influenced by concerns regarding tolerability^[4]. SAT is also increasingly used when curative surgical management is not feasible; however, it carries inherent risks, including cumulative toxicity and the lack of standardized monitoring protocols^[3,6]. Emerging evidence further suggests that discontinuation of chronic suppressive therapy following debridement, antibiotics, and implant retention (DAIR) may achieve outcomes comparable to those of continued suppression. This finding challenges assumptions regarding the necessity of prolonged therapy and raises additional concerns about cumulative antimicrobial toxicity^[16].

Despite increasing recognition of antimicrobial-related ADEs in PJI, the available evidence remains fragmented. Many studies inadequately report adverse events, use heterogeneous definitions and monitoring strategies, or focus primarily on

treatment efficacy rather than safety. These limitations hinder comprehensive assessment of the incidence, spectrum, and determinants of antimicrobial toxicity in this population.

Given the pivotal role of antimicrobial therapy in PJI management, a comprehensive synthesis of evidence regarding associated ADEs is warranted. This review aims to provide an updated narrative overview of the incidence, spectrum, and therapeutic implications of antimicrobial-related ADEs in PJI, with particular emphasis on associated risk factors.

Materials and Methods

Literature Search Strategy

A literature search was conducted to identify relevant studies evaluating antimicrobial-associated adverse events in the management of PJIs. PubMed/MEDLINE, Embase, and the Cochrane Library were searched for studies published from January 2010 through September 2025. The search strategy combined Medical Subject Headings terms and free-text terms, including “*prosthetic joint infection*,” “*periprosthetic joint infection*,” “*antimicrobial adverse events*,” “*antibiotic toxicity*,” “*antibiotic-related complications*,” and “*side effects*.” Boolean operators (“AND” and “OR”) were used to optimize the sensitivity and specificity of the search.

The reference lists of included studies and recent systematic reviews were also manually screened to identify additional potentially eligible publications. The search was limited to English-language articles involving human subjects.

Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria:

- Population: Adult patients with PJI confirmed according to standard diagnostic criteria.
- Intervention: Any antimicrobial therapy administered for the treatment or suppression of PJI, including intravenous, oral, or chronic suppressive antibiotic regimens.
- Outcomes: Studies reporting the incidence, type, or therapeutic consequences of ADEs attributable to antimicrobial therapy.
- Study design: Randomized controlled trials (RCTs), prospective or retrospective cohort studies, case-control studies, and systematic reviews.

Exclusion criteria were as follows: (1) studies that did not involve PJI; (2) case reports; (3) studies that did not explicitly report ADEs; and (4) non-English-language publications.

Study Selection and Data Extraction

Two independent reviewers screened the titles and abstracts of identified studies for eligibility, followed by full-text evaluation of potentially relevant studies. Discrepancies were resolved through discussion and, when necessary, consultation with a third reviewer.

A standardized data extraction form was used to collect the following variables: study characteristics; antimicrobial regimens, including drug class, route of administration, and treatment duration; incidence and type of ADEs; severity grading, when available; and therapeutic consequences, including treatment modification or discontinuation.

Data Synthesis, Quality Assessment and Risk of Bias

Findings were synthesized according to antimicrobial class, with emphasis on the incidence, spectrum, risk factors, and

Table 1. Incidence, severity, and treatment modifications associated with antimicrobial-related adverse events in PJI.

Antimicrobials	Incidence of ADEs [†]	Severity	Treatment modification rate
Vancomycin ± Piperacillin–tazobactam ^[11]	12.6 % overall; highest with combination	20.4 % severe (CTCAE [‡] grade ≥3)	12.6 % required modification
Daptomycin ^[35]	7.8 %	Not reported	Not reported
Fluoroquinolones ^[27]	Not reported	7.8 % severe ADEs	35.6 % discontinued
Rifampin ± co-trimoxazole ^[10]	46 %	Predominantly mild to moderate; gastrointestinal tract most affected	6 % discontinued; 29 % dose adjustment
Clindamycin ± rifampin ^[36]	Not reported	Mild; diarrhea most frequently reported	14 % discontinued
Linezolid + rifampin + clindamycin ^[37]	40.9 %	22.7 % Grade 3 neutropenia, anemia, hyponatremia	Discontinuation of linezolid in severe ADEs (22.7 %)
Linezolid ^[28]	33 %	Not reported	9 % discontinued
β-lactams ^[3]	33.8 %	Not reported	18 % discontinued or switched
Suppressive therapy (TMP–SMX [§] and combinations) ^[30]	11.1–16.3 %	Not reported	Not specified

[†]ADE, adverse drug event; [‡]CTCAE, Common Terminology Criteria for Adverse Events; [§]TMP–SMX, trimethoprim–sulfamethoxazole.

therapeutic implications of antimicrobial-associated ADEs. Where appropriate, evidence from RCTs and prospective cohort studies was prioritized over that from retrospective observational studies to strengthen the interpretation of findings, while observational studies were retained to capture real-world safety data.

Methodological quality and potential sources of bias were considered during data interpretation rather than evaluated using a formal risk of bias scoring system. Particular attention was given to study design, sample size, completeness of ADE reporting, and the methods used to attribute adverse events to antimicrobial therapy. Studies that employed standardized causality assessment or toxicity grading systems, such as the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) system criteria or the Common Terminology Criteria for Adverse Events (CTCAE), were considered methodologically more robust.

Rationale for Narrative Review Design

Although several methodological features commonly associated with systematic reviews were incorporated, this study was intentionally conducted as a narrative review. This approach was selected for three main reasons. First, the objective was to provide an integrative, drug class-oriented synthesis of ADEs, their risk factors, and clinical implications rather than to generate pooled estimates of incidence. Substantial heterogeneity among the eligible studies in ADE definitions, severity grading, follow-up duration, patient populations, and antimicrobial regimens precluded meaningful quantitative synthesis. Second, attempting to derive aggregated incidence estimates under these conditions could have overstated the precision and comparability of the available evidence. A narrative synthesis therefore allowed qualitative integration and critical contextualization of findings across antimicrobial classes while preserving clinically relevant differences among studies. Third, the review incorporated complementary sources of evidence, including pharmacological reviews, pharmacovigilance reports, and clinical practice guidelines, which were essential for contextualizing drug class-specific toxicity profiles but would not typically meet the eligibility criteria for a formal systematic review. Nevertheless, methodological safeguards traditionally used in systematic reviews were retained to enhance the transparency and methodological rigor of the review process.

Classes of Antimicrobials and Their Adverse Events

Beta-lactams

Beta-lactams remain foundational agents for susceptible PJI cases. Adverse effects include hypersensitivity reactions, ranging from mild rash to life-threatening anaphylaxis^[10,17].

With prolonged therapy, hematologic toxicities, including neutropenia and thrombocytopenia, may occur. High-dose cephalosporins and carbapenems can cause neurotoxicity, particularly in patients with renal dysfunction^[10,11,17]. The use of broad-spectrum agents also significantly increases the risk of *Clostridioides difficile* infection, particularly among older patients^[18,19].

Glycopeptides

Vancomycin is widely used to treat PJIs caused by methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci but carries a significant risk of nephrotoxicity, reported in 5%-15% of patients, particularly with prolonged therapy or concomitant use of nephrotoxic agents^[10,11,16,20]. Infusion-related reactions, such as “red man syndrome,” are common but can generally be prevented through slow infusion and appropriate premedication^[16,21]. Hematologic toxicity, including neutropenia, is uncommon but has been reported during extended treatment courses^[11]. Teicoplanin is considered less nephrotoxic; however, robust comparative data in patients with PJI remain limited^[16,22].

Lipopeptides

Daptomycin is an alternative for patients who are intolerant of vancomycin and has demonstrated efficacy in PJI management. The most clinically relevant adverse event is myopathy, with creatine kinase (CK) elevation occurring in 2%-5% of cases and warranting weekly CK monitoring^[4,23]. Rarely, eosinophilic pneumonia can develop after 2-3 weeks of therapy, necessitating immediate discontinuation^[4,24,25]. Unlike rifampin, daptomycin has no major drug-drug interactions, making it a suitable option for patients with multiple comorbidities and concomitant medications^[4,25].

Rifamycins

Rifampin is an important component of therapy for staphylococcal PJIs because of its biofilm activity, but hepatotoxicity is a major limitation. Up to 20% of patients develop asymptomatic elevations in transaminase levels, whereas clinically significant hepatitis, although rare, may necessitate treatment discontinuation^[13,26]. Rifampin also strongly induces cytochrome P450 enzymes, resulting in clinically important interactions with anticoagulants, antiplatelet agents, and immunosuppressants^[4,13]. Gastrointestinal intolerance and rash may also contribute to treatment discontinuation, potentially compromising biofilm-active therapy^[6,10].

Fluoroquinolones

Fluoroquinolones, which are commonly combined with rifampin, are valued for their high oral bioavailability but

are associated with a broad range of toxicities. Reported neurologic toxicities include peripheral neuropathy and seizures, whereas musculoskeletal complications include tendinopathy and tendon rupture, particularly among older adults and patients receiving concomitant corticosteroid therapy^[16,27]. Additional concerns include dysglycemia and QT interval prolongation, the latter of which may limit their use in patients with underlying cardiac conduction abnormalities or a predisposition to arrhythmias^[16,27].

Oxazolidinones

Linezolid is used for multidrug-resistant gram-positive PJIs but is limited by hematologic toxicity, with thrombocytopenia occurring in up to 30% of patients after 14 days of therapy^[17,28,29]. Other adverse events include anemia and leukopenia, consistent with bone marrow suppression^[17,28,29]. Prolonged treatment is associated with peripheral and optic neuropathy, which may be related to mitochondrial toxicity; cases of lactic acidosis have also been reported^[17,28,29]. Tedizolid, which has a lower risk of hematologic toxicity, may offer a safer alternative; however, clinical evidence supporting its use in PJI remains limited^[17,28].

Trimethoprim–Sulfamethoxazole (TMP-SMX)

TMP-SMX is frequently used for long-term suppressive therapy. Its adverse effects include bone marrow suppression, manifested as leukopenia and thrombocytopenia, particularly with prolonged treatment courses^[30]. Severe cutaneous hypersensitivity reactions, including Stevens-Johnson syndrome, are rare but have been reported in orthopedic cohorts^[31]. Electrolyte abnormalities, particularly hyperkalemia, are also common among patients with renal impairment^[31].

Clindamycin

Clindamycin is primarily reserved for patients with beta-lactam allergies and susceptible infections. The most serious adverse event is *Clostridioides difficile* colitis, which is relatively common and potentially life-threatening^[18,32]. Other toxicities include hepatotoxicity and hypersensitivity syndromes, such as drug reaction with eosinophilia and systemic symptoms^[32,33].

Fosfomycin

Fosfomycin may be considered as part of salvage regimens for infections caused by multidrug-resistant organisms and is associated with electrolyte disturbances, including hypokalemia and hyponatremia, as well as gastrointestinal intolerance. Evidence supporting its use in PJIs remains limited and warrants further controlled evaluation^[34].

Incidence, Severity, and Treatment Modifications Associated with Antimicrobial-Related Adverse Events in PJIs

Antimicrobial therapy for PJI is associated with a substantial burden of ADEs. Across prospective and retrospective cohort studies, the reported overall incidence of ADEs ranges from 7.8% to 46%, with severe events accounting for 7.8%-20.4% of cases, depending on the antimicrobial regimen and treatment duration^[3,10,11,27,28,30,35-37].

Adverse event severity is commonly graded according to the CTCAE, version 5.0. Under this system, Grade 1-2 events are considered mild to moderate, Grade 3 events are severe and typically require treatment modification or discontinuation, and Grade 4-5 events are considered life-threatening or fatal, respectively^[11].

Table 1 summarizes the reported incidence, severity, and therapeutic consequences of antimicrobial-associated ADEs across antimicrobial agents used to treat PJI^[3,10,11,27,28,30,35-37]. Marked variability was observed among antimicrobial classes, with rifampin-based combination regimens consistently associated with the highest overall ADE rates, whereas daptomycin demonstrated the lowest reported rates^[10,35]. Treatment discontinuation or dose modification was most frequent with agents requiring closer safety monitoring, with dose adjustment required in up to 29% of patients receiving rifampin-containing regimens and treatment discontinuation reported in 22.7% of patients receiving a linezolid–rifampin–clindamycin combination because of severe hematological toxicity^[10,37]. Likewise, discontinuation rates reached 35.6% for fluoroquinolones and 18% for β -lactams, indicating that treatment-limiting toxicity is not restricted to a single antimicrobial class^[3,27].

Risk Factors for Adverse Events in PJI Therapy

The development of adverse events during antimicrobial therapy for PJI is influenced by a combination of patient-, treatment-, and infection-related factors. Identifying these risk factors is critical for individualizing antimicrobial regimens and improving patient safety.

Patient-Related Risk Factors

Advanced age and chronic comorbidities substantially increase the risk of antimicrobial toxicity. Older patients and those with underlying conditions such as hypertension, hepatic dysfunction, congestive heart failure, and coronary artery disease are particularly susceptible to nephrotoxicity, especially when treated with agents that undergo renal elimination. The increased susceptibility to acute kidney injury (AKI) in these populations likely reflects both reduced renal

reserve and altered pharmacokinetics^[10,12,38]. Obesity [body mass index (BMI) ≥ 30 kg/m²] is an independent predictor of antibiotic-associated ADEs and treatment failure. Alterations in pharmacokinetic and pharmacodynamic parameters in individuals with obesity, including an increased volume of distribution and variable drug clearance, may contribute to drug accumulation and toxicity^[10,12].

Treatment-Related Risk Factors

Drug-Related Risk Factors

The pharmacokinetic and pharmacodynamic properties of antimicrobial agents are important determinants of their toxicity risk. Vancomycin administration, particularly in combination with other antimicrobial agents such as piperacillin-tazobactam, is associated with an increased incidence of nephrotoxicity, particularly AKI. Concurrent use of these agents has been associated with synergistic nephrotoxic effects^[11,39]. Prolonged courses of rifampin therapy, frequently used as part of combination regimens, have been associated with gastrointestinal adverse effects, including nausea and diarrhea, as well as cutaneous manifestations such as rash. These toxicities may necessitate treatment modification, including dose adjustment or discontinuation^[10].

Treatment Duration and Adverse Events

The duration of antibiotic therapy in PJI management remains a critical determinant of both treatment efficacy and safety. Although prolonged regimens are intended to improve infection control, they may increase the risk of adverse events without providing additional clinical benefit.

Extending antibiotic treatment beyond 1 year has not demonstrated an incremental benefit over standard 6-week regimens following DAIR, nor has prolonged therapy been associated with a reduction in adverse events^[16]. Similarly, oral therapy extending beyond 12 months has not been shown to improve outcomes and may promote antimicrobial resistance^[40,41]. A systematic review and meta-analysis likewise found no significant difference in infection recurrence between short (4-12 weeks) and prolonged treatment courses, further highlighting the limited clinical utility of extended therapy^[41].

Shorter intravenous courses (<4 weeks) have demonstrated noninferiority to longer regimens for infection control, while being associated with fewer adverse effects and a reduced healthcare burden^[42,43]. Conversely, intravenous therapy exceeding 6 weeks for *Cutibacterium acnes* shoulder PJI was associated with a significantly increased complication rate, particularly among older adults^[44]. Prolonged rifampin-based regimens are also frequently associated with gastrointestinal intolerance and treatment discontinuation^[10].

SAT, often reserved for patients who are unsuitable for curative surgery, raises additional concerns regarding long-term tolerability. Evidence suggests that SAT is associated with higher adverse event rates than curative treatment approaches. In a systematic review of long-term SAT combined with DAIR, 15.4% of patients developed adverse effects, leading to premature treatment discontinuation in several cases^[45].

Administration Route Impact

The route of antibiotic administration is a key determinant of both efficacy and safety in the management of PJI. Emerging evidence indicates that oral antibiotic therapy is non-inferior to intravenous (IV) therapy for infection control while offering advantages in terms of safety and tolerability.

Multiple studies have demonstrated comparable treatment efficacy between oral and IV regimens, with oral therapy associated with fewer adverse events and avoidance of complications related to intravenous access^[46,47]. Intravenous vancomycin has consistently been associated with higher rates of nephrotoxicity and treatment discontinuation than oral agents or alternative IV options such as daptomycin^[11,23].

In revision shoulder arthroplasty, IV antibiotic use was associated with a higher incidence of adverse events than oral therapy^[48]. Likewise, a multicenter study of PJI following total knee arthroplasty found no significant difference in adverse event rates between prolonged oral therapy and initial IV treatment, supporting oral antibiotics as a safe and effective alternative^[41].

Knowledge Gaps and Future Directions

Despite the recognized importance of ADEs, their reporting in PJI studies remains limited. Clinical trials in this field primarily focus on efficacy outcomes, such as reinfection rates and implant survival, whereas ADEs are often treated as secondary or exploratory endpoints. Moreover, the lack of standardized definitions and reporting frameworks for antimicrobial-related ADEs makes comparisons across studies challenging. This limited availability of comprehensive safety data restricts clinicians' ability to balance therapeutic efficacy and tolerability when selecting antimicrobial regimens. Consequently, current clinical guidelines rely more heavily on microbiological rationale and limited efficacy data than on systematic evaluations of treatment safety. Developing a standardized consensus framework for reporting ADEs in PJI research is therefore a critical step toward optimizing treatment and improving patient safety.

A second major knowledge gap concerns the clinical consequences of ADEs. Adverse events frequently necessitate dose reductions, antimicrobial substitutions, or premature discontinuation of otherwise effective therapies^[11]. Such

modifications may increase the risk of infection relapse and reduce the likelihood of successful eradication. For example, penicillin-associated ADEs have been associated with higher rates of hospital readmission, postoperative anemia, blood transfusion, and secondary PJI among patients with antibiotic intolerance^[49].

Furthermore, the economic and healthcare impacts of ADEs remain insufficiently explored. Toxicity-related complications often require additional laboratory monitoring, specialist consultations, and unplanned readmissions, all of which contribute to increased healthcare utilization and costs.

Several strategies show promise for reducing the impact of ADEs in PJI management. First, oral step-down therapy can reduce complications associated with intravenous access and shorten hospital stays. The OVIVA trial demonstrated that oral antimicrobial therapy for complex bone and joint infections was non-inferior to prolonged intravenous treatment while significantly reducing catheter-associated complications and treatment burden^[50]. Second, accumulating evidence indicates that shorter antibiotic regimens may be sufficient in selected PJI cases, potentially reducing cumulative toxicity without compromising efficacy^[41]. Third, long-acting antimicrobials, such as dalbavancin, which has an extended half-life and favorable safety profile, have been successfully used off-label for bone and joint infections. These agents may improve adherence and reduce treatment discontinuation related to ADEs^[51,52].

Finally, individualized therapeutic approaches that integrate therapeutic drug monitoring, assessment of host-related factors, and precision dosing may enable clinicians to maximize treatment efficacy while minimizing toxicity.

Study Limitations

This review has several limitations that warrant consideration. First, despite the implementation of methodological safeguards to enhance transparency and reproducibility, the narrative design precluded formal quantitative synthesis, including pooled estimates of ADE incidence and quantitative benefit-risk analyses, and did not eliminate the potential for selection and reporting bias. Second, substantial heterogeneity in ADE definitions, severity grading systems, patient populations, antimicrobial regimens, follow-up durations, and reporting practices limited direct comparisons across studies and likely contributed to the wide range of reported overall ADE incidence. Third, the available evidence was derived predominantly from retrospective, single-center observational studies with variable sample sizes and methodological quality. Furthermore, relatively few studies applied standardized causality assessment tools, such as the WHO-UMC system or the Naranjo algorithm, to establish the

relationship between antimicrobial exposure and reported ADEs, increasing the potential for misclassification of adverse events. Fourth, publication and reporting biases may have resulted in underreporting of mild or subclinical ADEs, whereas clinically significant events requiring treatment modification or discontinuation were more likely to be documented. RCTs, systematic reviews, and meta-analyses using standardized outcome definitions are therefore needed to generate more precise estimates of ADE incidence and quantify the benefit–risk profile of individual antimicrobial regimens.

Conclusion

Antimicrobial-related ADEs represent a significant yet underrecognized challenge in the management of PJIs. Across clinical studies, ADEs affect up to 46% of patients and frequently necessitate treatment modification or discontinuation. Vancomycin–piperacillin–tazobactam combinations are associated with the highest risk of nephrotoxicity, whereas rifampin and linezolid are major contributors to hepatotoxic and hematologic toxicity, respectively. Patient-specific factors, including advanced age, renal impairment, obesity, and polypharmacy, further increase susceptibility to severe ADEs. Increasing evidence supports shorter and orally administered antimicrobial regimens that can maintain infection control while minimizing toxicity and healthcare burden.

Future clinical research should prioritize standardized ADE reporting frameworks and incorporate safety endpoints into PJI treatment trials. The adoption of precision dosing, therapeutic drug monitoring, and novel long-acting antimicrobials may further improve treatment safety. Overall, a patient-centered, evidence-based approach that balances antimicrobial efficacy with tolerability is critical for optimizing clinical outcomes while minimizing treatment-related harm in patients with PJIs.

Footnotes

Authorship Contributions

Concept: O.S., H.E., Design: O.S., H.E., Analysis or Interpretation: O.S., H.E., H.L., I.K., M.M., L.A., Literature Search: O.S., H.E., Writing: O.S., H.E., H.L., I.K., M.M., L.A.

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