

Understanding the risk and therapeutic possibilities for periprosthetic joint infections: a comprehensive review

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ABSTRACT

Aim: To summarize the current evidence on risk factors, microbiological profiles, and treatment complications associated with PJIs. By synthesizing findings from recent studies, this review identifies key challenges and areas for improvement in the prevention, diagnosis, and management of PJIs.

Materials and Methods: A comprehensive literature search was conducted across major academic databases, including PubMed, Embase, and Web of Science, to identify relevant articles published between 2015 and 2025. Studies were selected based on their focus on microbial, biomechanical, and patient-related factors influencing PJI outcomes.

The review highlights the predominance of Gram-positive bacteria, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, as major pathogens in PJIs, with an increasing role of *Candida* species in complex cases. Key patient-related risk factors include obesity, diabetes, advanced age, and immunosuppression. Two-stage revision arthroplasty remains the gold standard for managing chronic PJIs, though single-stage revisions are gaining attention for specific scenarios. Emerging diagnostic biomarkers, such as calprotectin, offer potential for earlier and more accurate diagnosis, while advancements in biofilm-targeted therapies represent promising directions for treatment.

Conclusions: PJIs represent a multifaceted clinical challenge requiring a multidisciplinary approach. Current knowledge underscores the importance of individualized patient optimization, standardized diagnostic protocols, and targeted antimicrobial strategies. Future research should focus on addressing knowledge gaps in diagnostic biomarkers, biofilm management, and the optimization of surgical approaches to improve patient outcomes and reduce the burden of PJIs.

KEY WORDS: periprosthetic joint infection, total joint arthroplasty, microbial pathogens, two-stage revision, diagnostic biomarkers, infection management

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INTRODUCTION

Periprosthetic joint infection (PJI) is a severe complication following total joint arthroplasty (TJA), occurring in approximately 1–2% of primary hip and knee replacements. PJIs significantly impact patient morbidity, healthcare expenditures, and mortality rates [1]. Although bacterial pathogens, particularly *Staphylococcus aureus* and *Staphylococcus epidermidis*, are predominant causative organisms, fungal PJIs, primarily involving *Candida* species, present unique diagnostic and therapeutic challenges despite their relatively low prevalence (around 1%) [2].

Candida albicans is the most frequently identified fungal pathogen in PJIs; however, non-*albicans Candida* species, such as *Candida parapsilosis* and *Candida tropicalis*, have been increasingly recognized as clinically significant [3–5]. Fungal PJIs often occur in a polymicrobial setting, complicating their diagnosis and management. They are also commonly associated with patient-related

risk factors, including diabetes mellitus, immunosuppression, and multiple revision surgeries [6, 7].

The gold-standard treatment for chronic PJIs, including fungal infections, typically involves a two-stage revision arthroplasty - removal of the infected implant, extensive debridement, insertion of an antibiotic-loaded spacer, and subsequent reimplantation [8, 9]. Nevertheless, fungal PJIs generally have poorer clinical outcomes compared to bacterial infections, characterized by higher recurrence rates, longer hospitalization periods, and lower rates of infection-free survival [10]. Additionally, variability in management strategies persists, with some advocating single-stage revision procedures or implant retention in select scenarios [11].

Current literature predominantly focuses on bacterial PJIs, leading to a gap in high-quality evidence specifically addressing differences in clinical outcomes, therapeutic responses, and prognoses between *Candida albicans*

and non-albicans *Candida* species infections [12, 13]. Bridging this gap is critical for the development of improved clinical guidelines and optimized patient care.

AIM

The main aim of this narrative review is to provide a comprehensive overview of periprosthetic joint infections (PJIs), with particular emphasis on fungal infections caused by *Candida albicans* and non-albicans *Candida* species. Specifically, the review aims to: (1) Compare clinical outcomes of PJIs caused by *Candida albicans* versus non-albicans *Candida* strains, focusing on infection-free survival, recurrence rates, and surgical results. (2) Identify and summarize key risk factors associated with fungal PJIs, including patient demographics, comorbidities, and previous surgical history, as well as highlight important contributing factors to PJIs in general, such as obesity, diabetes, and operative conditions. (3) Evaluate current treatment strategies for fungal PJIs, particularly the effectiveness of single-stage versus two-stage revision surgeries and antifungal therapy. (4) Highlight existing knowledge gaps in the management of fungal PJIs and suggest directions for future research, particularly emphasizing the need for development of biofilm-active antifungal agents and standardized clinical guidelines. While the primary focus of this review is on fungal PJIs, additional clinically relevant factors - including bacterial etiologies, surgical factors, and patient-specific risk profiles - are also summarized briefly and systematically to provide comprehensive context.

MATERIALS AND METHODS

SEARCH STRATEGY

The search strategy for this narrative review was designed to comprehensively identify relevant studies on PJIs, specifically fungal PJIs caused by *Candida albicans* and non-albicans *Candida* strains. We searched major academic databases including: PubMed/MEDLINE, Scopus, Embase, Web of Science, and Cochrane Library. A combination of MeSH terms and keywords was used to capture all relevant studies: "Periprosthetic joint infection" OR "PJI" OR "Fungal infection" OR "*Candida*" OR "*Candida albicans*" OR "non-albicans *Candida*" OR "Total hip arthroplasty" OR "Total knee arthroplasty" OR "Revision surgery" OR "Two-stage revision" OR "Single-stage revision" OR "Antifungal therapy" OR "Polymicrobial infection"

QUALIFICATION CRITERIA

Inclusion criteria: studies published in peer-reviewed journals from 2015 to 2024. Articles in English. Studies

that examined fungal PJIs in patients undergoing total joint arthroplasty, specifically those infected with *Candida* species. Articles reporting clinical outcomes, risk factors, or treatment strategies for fungal PJIs. Exclusion Criteria: articles focusing solely on bacterial PJIs without discussing fungal infections. Studies involving animal models or in vitro research without clinical application. Case reports with insufficient data or outcome measures.

DATA EXTRACTION

Initial screening was performed by reviewing titles and abstracts. Full-text articles were subsequently reviewed to ensure relevance. Reference lists of relevant articles were also screened to capture any additional studies missed in the primary search. Data was extracted from each article on the study design, patient population, infection type, surgical methods (one-stage vs. two-stage), antifungal therapy used, clinical outcomes (e.g., infection-free survival, recurrence rates), and conclusions.

REVIEW

After a comprehensive database search, 23 research trials and 11 review papers and/or meta-analyses were included in this review, all contributing to the understanding of PJIs, particularly those involving fungal pathogens. The selected studies provide valuable insights into the multifactorial risk factors, diagnostic challenges, and treatment outcomes associated with PJIs. Key findings emphasize the predominance of Gram-positive bacteria such as *Staphylococcus aureus*, alongside the increasing recognition of *Candida* species as significant pathogens in complex, polymicrobial infections. Individual risk factors, including advanced age, diabetes, high body mass index (BMI), and chronic illnesses, further exacerbate infection risks, complicating the management of PJIs. Operative factors, such as prosthesis type and intraoperative contamination, also play a crucial role in infection rates, particularly in revision surgeries. Treatment outcomes favor two-stage revision surgeries, which demonstrate higher infection-free survival, although cases involving fungal or polymicrobial infections often result in poorer prognoses and higher recurrence rates.

In this review, the studies have been grouped thematically according to key issues related to periprosthetic infections:

- Risk factors (BMI, diabetes) [17, 18, 21-23, 25, 31, 37, 42, 46],
- Bacterial infections [14, 15-17, 19, 23, 32-35, 39, 43, 45],
- Fungal infections (*Candida albicans* and non-albicans) [3, 4, 5, 7, 12, 13, 27, 29, 35],
- Surgical revisions and surgical treatment strategies [16, 20, 27, 28, 30, 33, 34, 38, 41].

Table 1. Summary of the research papers on PJI risk factors

No.	Authors, year	Journal	Study type	Study group	Study aim	Risk factors	Results
1	Guo, H. et al., 2020 [14]	<i>Journal of Infection in Developing Countries</i>	Case-control	96 PJIs, 192 controls	Explore PJI risk factors	Microbiological, Individual	Gram-positive bacteria common (76.19%), <i>S. aureus</i> in knees
2	Lee, Mak, Wong, 2015 [15]	<i>Journal of Orthopaedic Surgery</i>	Case-control	1133 TKAs, 8 PJIs	Incidence, risk factors in TKAs	Microbiological, Individual, Operating	<i>S. aureus</i> , <i>coagulase-negative staph</i> prevalent
3	Erivan et al., 2017 [16]	<i>Orthopaedics & Traumatology: Surgery & Research</i>	Retrospective	26 PJIs	Manage spacer-related complications	Microbiological, Biomechanical	78% Gram-positive cocci, high spacer complications
4	Papalia et al., 2019 [17]	<i>European Review for Medical and Pharmacological Sciences</i>	Case-control	28 PJI, 84 controls	Assess incidence, risk factors	Individual (BMI, diabetes), Microbiological	<i>S. aureus</i> and <i>polymicrobial infections</i> common
5	Yilmaz et al., 2020 [18]	<i>BMC Musculoskeletal Disorders</i>	Retrospective	57 octogenarians	Outcome of PJI in elderly	Individual (age, BMI)	86% chronic infections; high BMI in cases
6	Ibrahim et al., 2018 [19]	<i>Bone & Joint Journal</i>	Comparative	50 culture-positive vs negative	Culture-negative vs positive PJIs	Microbiological, Individual	<i>S. epidermidis</i> dominant, <i>antibiotics impact</i>
7	Kingsbury et al., 2022 [20]	<i>Bone & Joint Journal</i>	Cross-sectional	568 revisions	Revision routes and symptoms	Individual (age)	Younger patients, better outcomes
8	Velez de Lachica et al., 2022 [21]	<i>J ISAKOS</i>	Prospective	83 PJIs	Compare vancomycin-loaded vs control	Individual (BMI, diabetes)	CRP/ESR elevated, PJI higher with high BMI
9	Lenguerrand et al., 2018 [22]	<i>Lancet Infectious Diseases</i>	Cohort	623,253 hips	Risk factors for hip revisions	Patient-related, Surgical	High BMI, diabetes, pulmonary disease increased PJI risk
10	Lenguerrand et al., 2019 [23]	<i>Lancet Infectious Diseases</i>	Cohort	679,010 knees	Risk factors for knee PJI	Patient-related, Surgical	Obesity, diabetes, prior infection, cemented replacements risk
11	Vasiliadis et al., 2021 [24]	<i>Cureus</i>	Case series	4 patients	Effectiveness of DAIR in PJIs	Laboratory, Surgical	High success in treating Acinetobacter PJIs
12	Panula et al., 2021 [25]	<i>Acta Orthopaedica</i>	Cohort	33,337 THAs	Risk factors in Finnish registry	Patient, Surgical	High BMI, ASA grade, bleeding >500mL risks
13	Watanabe et al., 2021 [26]	<i>Journal of Orthopaedic Surgery and Research</i>	Cross-sectional	109 PJIs	Risk factors for culture-negative PJIs	Laboratory, Microbiological	CRP, ESR levels predictive, <i>S. epidermidis</i> common
14	Gao et al., 2018 [27] 25-129 months	<i>Medical Science Monitor</i>	Retrospective	18 fungal PJIs	Success rate in fungal PJIs	Microbiological, Laboratory	<i>Candida species</i> common; 2-stage revision success rates moderate
15	Singh et al., 2016 [28]	<i>Canadian Journal of Surgery</i>	Registry	930 THAs, 734 TKAs	Revision patterns post-registry	Surgical	Registry reduced early revision rates
16	Leitner et al., 2020 [29]	<i>Journal of Arthroplasty</i>	Retrospective	135 FA cases	Evaluate site-specific factors	Individual, Microbiological	Nicotine abuse, multiple revisions increased FA risk
17	Newman et al., 2018 [30]	<i>Journal of Arthroplasty</i>	Randomized	160 revisions	ciNPWT vs standard care	Microbiological	ciNPWT reduced complications in high-risk revisions

Table 1. Cont.

18	Bae et al., 2022 [31]	<i>Joint Diseases and Related Surgery</i>	Retrospective	12,320 TJAs	Incidence and risk factors in TJAs	Individual	Hypertension, UTI, prior corticosteroids risk factors
19	Li et al., 2021 [32]	<i>BMC Musculoskeletal Diseases</i>	Cohort	64 polymicrobial, 158 monomicrobial PJIs	Polymicrobial PJI risk factors	Microbiological, Individual	Streptococcus, Enterococcus, Gram-negative species prevalent
20	Steinicke et al., 2023 [33]	<i>Archives of Orthopaedic and Trauma Surgery</i>	Retrospective	55 PJIs	Success rates of 2-stage revision	Microbiological, Surgical	High success, but obesity and <i>S. epidermidis</i> linked to failures
21	Metcalfe et al., 2023 [34]	<i>Antibiotics</i>	Retrospective	470 revisions	Outcomes between one- and two-stage revisions	Microbiological	<i>S. aureus</i> and MSSA frequent in failed revisions
22	Wingert et al., 2016 [35]	<i>Clinical Orthopaedics and Related Research</i>	Prospective	1,536 TJAs	Accuracy of NSQIP in predicting infections	Post-op	NSQIP effective for predicting 30- and 90-day infections
23	Karczewski et al., 2022 [35]	<i>International Orthopaedics</i>	Retrospective	29 Candida PJIs	Candida PJI outcomes	Microbiological, Laboratory	<i>Candida albicans</i> vs non- <i>albicans</i> PJIs analyzed, moderate success with antifungal therapy

Abbreviations: BMI, body mass index; THA, total hip arthroplasty; TKA, total knee arthroplasty; PJI, periprosthetic joint infection; ASA, American Society of Anesthesiologists; CRP, C-reactive protein; ERS, erythrocyte sedimentation rate; ciNPWT, Closed-incision negative-pressure wound therapy; UTI, urinary tract infection; methicillin-sensitive *Staphylococcus aureus*; NSQIP, National Surgical Quality Improvement Program

Source: compiled by the authors of this study

RESEARCH TRIALS

Table 1 shows the research trials on PJI risk factors.

Guo et al. [14] conducted a case-control study among 96 patients who developed PJIs after receiving primary artificial joint replacements and 192 control patients who underwent similar surgeries but did not develop infections. It was demonstrated that older patients and those with compromised immune systems were at higher risk of developing PJIs. Furthermore, differences in infection patterns were observed between hip and knee arthroplasty patients, suggesting that anatomical and procedural factors may influence the risk of infection.

Lee, Mak, and Wong (2015) [15] conducted a case-control study including a total of 1,133 TKA procedures performed between 2000 and 2014, out of which 8 cases (0.71%) developed PJIs. The study suggested that longer operative durations may increase the likelihood of intraoperative contamination, particularly in cases where optimal sterile conditions are difficult to maintain for extended periods. This finding emphasizes the need for meticulous infection control protocols during surgery and highlights the potential benefit of reducing operative time wherever possible.

Erivan et al. (2017) [16] conducted a retrospective study focusing on the management of complications related to the use of antibiotic-loaded spacers in two-stage revision surgeries for chronic PJIs. The study high-

lighted the need for careful selection and placement of spacers, especially in patients at higher risk of mechanical complications. It also underscored the importance of balancing the mechanical stability of spacers with the need for effective local antibiotic delivery, as complications can lead to delays in infection control and complicate the second-stage reimplantation process.

Papalia et al. (2019) [17] total Hip arthroplasty (THA) conducted a case-control study on 28 patients who developed PJIs and 84 control patients who underwent similar procedures but did not develop infections. The study emphasized that the presence of multiple microorganisms in PJI cases complicates both diagnosis and treatment, as managing mixed bacterial populations requires broader-spectrum antibiotic regimens and may lead to prolonged recovery times.

Yilmaz et al. (2020) [18] investigated the outcomes of PJIs in a cohort of 57 octogenarians. The findings underscore the importance of optimizing preoperative risk factors, such as weight management, particularly in elderly populations where these factors exacerbate the complexity of infection management. Yilmaz et al. [18] further emphasize the need for tailored treatment strategies in elderly patients with PJIs, suggesting that more aggressive treatment approaches, such as two-stage revisions, may be necessary to improve infection control in this vulnerable group.

Ibrahim et al. (2018) [19] included 100 patients, 50 of whom had culture-positive PJIs and 50 with cul-

ture-negative PJIs. The study emphasized the importance of optimizing preoperative antibiotic protocols to prevent the emergence of culture-negative PJIs. Additionally, it underscored the need for advanced diagnostic tools, such as molecular techniques, to improve the detection of pathogens in culture-negative cases, which remain challenging to manage effectively.

Kingsbury et al. (2022) [20] conducted a cross-sectional study on 568 revision cases, with a primary focus on understanding how patient age and other individual factors influenced the success of revision surgeries and overall outcomes. This study underscores the importance of considering age and comorbidities when planning revision surgeries for PJIs, as these factors significantly impact the likelihood of success. Tailored approaches that take into account the patient's age, physical condition, and medical history may improve outcomes in revision surgeries for PJIs, particularly in older populations.

Velez de Lachica et al. (2022) [21] conducted a prospective study involving 83 patients undergoing revision procedures for PJIs, with a focus on identifying how patient-specific factors such as BMI and diabetes impacted infection rates and outcomes. The study indicated that obesity and diabetes were important individual risk factors that increased the likelihood of postoperative infections. Patients with a high BMI had a disproportionately higher incidence of PJIs, further supporting the need for targeted infection prevention strategies in this group.

Lenguerrand et al. (2018) [22] surgical, and health-care factors. Existing evidence is based on short-term follow-up. It does not differentiate between factors associated with early onset caused by the primary intervention from those associated with later onset more likely to result from haematogenous spread. We aimed to assess the overall and time-specific associations of these factors with the risk of revision due to PJI after primary total hip replacement. \nMETHODS: We did a prospective observational cohort study analysing 623 253 primary hip procedures performed between April 1, 2003, and Dec 31, 2013, in England and Wales and recorded the number of procedures revised because of PJI. We investigated the associations between risk factors and risk of revision for PJI across the overall follow-up period using Poisson multilevel models. We reinvestigated the associations by post-operative time periods (0-3 months, 3-6 months, 6-12 months, 12-24 months, >24 months analyzed data from 623,253 hip replacements performed in England and Wales, making it one of the largest datasets ever studied for this purpose. The study suggested that impaired lung function could affect the patient's overall resilience to

infection and complicate their recovery following surgery. Surgical factors, including the complexity of the revision procedure and the use of cemented implants, were also associated with higher infection rates. The study highlighted that longer operative times and more complex surgeries increase the risk of intraoperative contamination and postoperative complications, which further contribute to the development of PJIs.

Lenguerrand et al. (2019) [23] surgical, and health-care system factors. Existing evidence is limited by heterogeneity in populations studied, short follow-up, inadequate power, and does not differentiate early prosthetic joint infection, most likely related to the intervention, from late infection, more likely to occur due to haematogenous bacterial spread. We aimed to assess the overall and time-specific associations of these factors with the risk of revision due to prosthetic joint infection following primary knee replacement. \nMETHODS: In this cohort study, we analysed primary knee replacements done between 2003 and 2013 in England and Wales and the procedures subsequently revised for prosthetic joint infection between 2003 and 2014. Data were obtained from the National Joint Registry linked to the Hospital Episode Statistics data in England and the Patient Episode Database for Wales. Each primary replacement was followed for a minimum of 12 months until the end of the observation period (Dec 31, 2014) conducted a large cohort study and analyzed an extensive dataset comprising 679,010 knee arthroplasty procedures, making it one of the largest studies to assess patient-related and surgical factors contributing to PJIs in TKA. The study suggested that cemented replacements may increase the risk of infection due to the potential for intraoperative contamination and the challenges of achieving optimal cement fixation in certain patients.

Vasiliadis et al. (2021) [24] we aimed to investigate the effectiveness of debridement, antibiotics, irrigation, and implant retention (DAIR, in a case series reported high success in treating these PJIs, with all four patients achieving infection control following DAIR. They demonstrated that DAIR can be a viable option for managing PJIs, particularly in cases where the pathogen is well-characterized and antibiotic therapy can be carefully selected. The study advocates for further research with larger cohorts to validate the findings and assess long-term outcomes of DAIR in PJIs involving multidrug-resistant organisms like *Acinetobacter*.

Panula et al. (2021) [25] we assessed risk factors for PJI after primary total hip arthroplasty (THA) utilized data from 33,337 THA procedures performed between 2002 and 2013. The study recommended that surgical teams take measures to minimize blood loss during THA pro-

cedures, such as using advanced hemostatic techniques or considering strategies like intraoperative blood salvage. They emphasized the importance of addressing modifiable risk factors, such as obesity and blood loss, to reduce the incidence of PJs in THA patients. They also called for individualized care plans based on patient health status, as indicated by ASA grades, to improve outcomes and minimize infection risks.

Watanabe et al. (2021) [26] examined 109 patients with PJs, comparing culture-negative cases with culture-positive ones to identify specific risk factors and laboratory markers that could aid in the diagnosis of culture-negative PJs. The authors suggested that many culture-negative PJs may be due to biofilm-forming bacteria like *S. epidermidis*, which are difficult to detect using conventional culture techniques. They emphasized the need for advanced diagnostic methods, such as molecular testing and next-generation sequencing, to improve pathogen detection in culture-negative PJs. These techniques could enhance diagnostic accuracy and allow for more effective, targeted treatment in cases where standard cultures are inconclusive.

Gao et al. (2018) [27] 25-129 months involved 18 cases of fungal PJs, with the primary aim of assessing the microbiological profiles and clinical outcomes associated with these challenging infections. They reported moderate success rates for two-stage revision surgeries in treating fungal PJs. While the two-stage approach, involving the removal of the infected prosthesis, placement of an antibiotic-impregnated spacer, and eventual reimplantation, remains the gold standard for managing PJs, fungal infections posed additional challenges. The overall success rates were lower compared to bacterial PJs, reflecting the complexity of treating fungal organisms and the need for prolonged antifungal therapy.

Singh et al. (2016) [28] utilized data from 930 THAs and 734 TKAs, with the goal of assessing how the implementation of joint replacement registries influenced early revision rates in these procedures. From a surgical perspective, the study emphasized that registries serve as a critical tool for improving the quality of arthroplasty procedures. Surgeons were able to use registry data to track patient outcomes and identify specific factors associated with revision, such as implant failure, infection, or technical complications during surgery. This feedback loop allowed for continuous improvement in surgical practices, ultimately lowering the rates of revision surgeries within the first few years postoperatively.

Leitner et al. (2020) [29] analyzed 135 cases of FA to determine site-specific and individual risk factors that contributed to the development of this challenging condition. They demonstrated that nicotine abuse and

multiple revision surgeries are key risk factors for FA in joint arthroplasty patients. The findings underscore the importance of preoperative counseling on smoking cessation and careful surgical planning in patients with a history of multiple revisions to reduce the risk of fungal infections.

Newman et al. (2018) [30] involved 160 revision surgeries, with the primary aim of evaluating whether ciNPWT could lower the risk of complications in high-risk patients. They found that ciNPWT was more effective than standard wound care in reducing postoperative complications in high-risk revision surgeries for PJs. The study supports the use of ciNPWT as a valuable tool for improving outcomes in patients undergoing revision procedures, particularly those with elevated infection risk.

Bae et al. (2022) [31] including demographic features, comorbidities, prior corticosteroid usage, and preoperative laboratory values. Results There were 34 revision TJAs as a consequence of PJI (hip, 16; knee, 18 analyzed data from 12,320 TJA procedures to identify individual patient risk factors that contribute to an increased likelihood of developing PJs. They concluded that hypertension, UTIs, and prior corticosteroid use were significant risk factors for PJs in TJA patients. The study emphasized the need for preoperative risk assessment and management of these conditions to reduce the likelihood of infections and improve surgical outcomes.

Li et al. (2021) [32] included 64 cases of polymicrobial PJs and 158 cases of monomicrobial PJs, focusing on microbiological profiles and individual patient risk factors that contributed to these infections. I was highlighted the distinct challenges associated with polymicrobial PJs, particularly due to the prevalence of *Streptococcus*, *Enterococcus*, and Gram-negative bacteria. The study emphasized the importance of identifying high-risk patients and tailoring antimicrobial therapies to address the complexity of these infections.

Steinicke et al. (2023) [33] management of recurrent infection after a two-stage exchange remains debated and the outcome of a repeat two-stage procedure is unclear. This study investigates the success rates of repeat two-stage exchange arthroplasty and analyzes possible risk factors for failure. Materials and methods We retrospectively identified 55 patients (23 hips, 32 knees included 55 patients who underwent two-stage revisions, focusing on microbiological profiles and surgical factors that influenced the outcomes. The study suggested that obesity creates a more challenging environment for infection control, highlighting the need for preoperative weight management strategies to improve surgical success. They demonstrated that while two-stage revision remains an effective approach for managing PJs, the presence of *S. epidermidis* and patient factors such as obesity can significantly impact treatment success. The

Table 2. Summary of the reviews and meta-analyses on PJI risk factors

No.	Authors, year	Journal	Design	Participants	Study aim	Key findings
1	Kong et al., 2017 [36]	<i>International Wound Journal</i>	Meta-analysis	3,561,446 hips (40 studies)	Identify risk factors for PJIs post-THA	Higher BMI, diabetes, rheumatoid arthritis, and AVN are key risk factors for PJIs after THA.
2	Ren et al., 2021 [37]	<i>BMC Musculoskeletal Disorders</i>	Meta-analysis	40 studies (various regions)	Patient-related PJI risk factors in THA	High BMI, diabetes, chronic pulmonary disease, and RA were significant risk factors for PJIs.
3	Mian et al., 2022 [38]	<i>BMC Musculoskeletal Disorders</i>	Review	NS	Review of current debridement practices for PJIs	Biofilm eradication is critical for successful PJI debridement; two-stage revision remains the gold standard.
4	Rottier et al., 2023 [39]	<i>Journal of Bone & Joint Surgery</i>	Review	NS	Principles of antimicrobial treatment in PJIs	Biofilm-active antibiotics like rifampicin and fluoroquinolones are essential in treating Gram-positive and Gram-negative PJIs.
5	Schindler et al., 2023 [40]	<i>Journal of Arthroplasty</i>	Systematic review	19 studies	Novel diagnostic biomarkers for PJIs	Calprotectin shows high sensitivity and specificity for early PJI diagnosis.
6	Zhao et al., 2024 [41]	<i>Clinical Orthopaedics and Related Research</i>	Meta-analysis	8,711 revisions (40 studies)	Compare single-stage vs. two-stage revision	No significant difference in reinfection/reoperation rates between single- and two-stage revisions.
7	Rodriguez-Merchan et al., 2022 [42]	<i>Journal of Clinical Medicine</i>	Narrative review	NS	Overview of TKA PJI risk factors	An increased risk of PJI is associated with factors such as male sex, younger age, and pre-existing conditions like type II diabetes, class II obesity, rheumatoid arthritis, and hypertension. Procedural and postoperative factors, including prolonged operative time, use of blood transfusions, patellar resurfacing, and prolonged hospital stays, also contribute to higher infection rates.
8	Tsikopoulos et al., 2023 [43]	<i>Antibiotics</i>	Narrative review	NS	Review PJI diagnostic markers	Determining the bacterium that caused the infection is essential to implement the antibiotics, long-term treatment, and prognosis for PJIs patients.
9	Almeida et al., 2021 [44] and persistent wound drainage (PWD)	<i>EFORT Open Reviews</i>	Narrative review	75 articles	Review PWD and risk factors	Smoking, obesity, anemia linked to PWD
10	Dobson, Reed, 2020 [45]	<i>EFORT Open Reviews</i>	Review	119 articles	Infection reduction in primary THA/TKA	The risk of SSI and PJI is related to surgical factors and patient factors such as age, BMI, co-morbidities, and lifestyle.
11	Alamanda et al., 2021 [46]	<i>EFORT Open Reviews</i>	Review	75 articles	Review PWD and risk factors	Factors minimizing risk of PJIs: better postoperative glycemic control, appropriate treatment of obesity, malnutrition, metabolic syndrome, preoperative anemia and smoking abstinence.

Abbreviations: NS, not specified; BMI, body mass index; THA, total hip arthroplasty; RA, rheumatoid arthritis; PJI, periprosthetic joint infection; PWD, persistent wound drainage; AVN, avascular necrosis; SSI, surgical site infection
Source: compiled by the authors of this study

study emphasized the importance of addressing both microbiological and individual risk factors to improve outcomes in patients undergoing two-stage revisions. Metcalf et al. (2023) [34] males have a higher rate of revision. The literature lacks studies examining the relationship between sex and outcomes following single and two-stage exchange for periprosthetic joint infection (PJI analyzed 470 revision cases to determine

the effectiveness of each approach and identify microbiological factors associated with failed revisions. It was demonstrated that two-stage revisions tend to yield better outcomes for PJIs caused by *S. aureus* and MSSA. The study emphasized the importance of considering microbiological factors when selecting the appropriate revision strategy to improve success rates and reduce the likelihood of recurrent infections.

Wingert et al. (2016) [35] analyzed data from 1,536 TJA procedures to assess how effectively NSQIP could predict 30- and 90-day postoperative infections. The study highlighted the value of NSQIP not only in infection prediction but also in enhancing overall quality improvement efforts in TJA procedures. In conclusion, NSQIP is an effective tool for predicting 30- and 90-day postoperative infections, including PJIs, in patients undergoing TJA. The study emphasized the importance of using data-driven approaches, such as NSQIP, to improve patient outcomes and reduce postoperative complications.

Karczewski et al. (2022) [35] included 29 cases of *Candida* PJIs, with the goal of comparing the outcomes of infections caused by *Candida albicans* versus non-*albicans* species, as well as assessing the success of antifungal therapies. Laboratory findings revealed that elevated CRP and other inflammatory markers were present in most *Candida* PJIs, aiding in the diagnosis of these infections. Antifungal therapy, particularly the use of azoles, demonstrated moderate success in treating *Candida* PJIs. However, the study noted that outcomes were generally better in *Candida albicans* infections compared to non-*albicans* species, which tend to be more resistant to standard antifungal treatments. They highlighted the complexity of managing *Candida* PJIs, particularly those caused by non-*albicans* species. While antifungal therapy can be effective, success rates remain moderate, and a combination of surgical debridement and targeted antifungal treatment is often necessary to achieve infection control.

REVIEWS AND META-ANALYSES

Table 2 shows reviews and meta-analyses on PJI risk factors.

Kong et al. (2017) [36] included data from 24 studies, which encompassed a wide range of patient characteristics, surgical factors, and postoperative outcomes. The study highlighted prolonged surgical duration as a major contributor to infection risk. Extended operative times increase the likelihood of intraoperative contamination, as sterile fields become more challenging to maintain over time. Prolonged surgeries also lead to greater tissue trauma and exposure, which further elevates the risk of infection. The authors emphasized the importance of minimizing surgical time without compromising procedural outcomes to reduce the likelihood of PJIs.

Ren et al. (2021) [37] analyzed 40 studies, involving a total of 3.5 million hip arthroplasties, making this one of the largest meta-analyses focused on PJI risk factors in THA. The study identified several modifiable

patient-related risk factors that were strongly associated with the occurrence of PJIs. High BMI was a leading risk factor, with obese patients exhibiting a significantly higher likelihood of developing infections. The study suggested that obesity impairs wound healing and promotes inflammation, both of which increase the risk of postoperative infections. Diabetes was another major factor linked to PJIs in THA patients. Poor glycemic control was particularly associated with elevated infection risk, as hyperglycemia can weaken the immune system and delay the healing process.

Mian, Samuel, and Hurley (2022) [38] published a comprehensive review emphasizing the significance of aggressive surgical debridement combined with systemic and local antimicrobial therapy in treating PJIs. One of the key challenges highlighted in the review is the role of biofilms in chronic infections, which necessitates mechanical removal for effective eradication. The gold standard for chronic PJIs, according to the review, remains two-stage revision arthroplasty. This approach involves the removal of the infected prosthesis, the use of an antibiotic-impregnated spacer, and reimplantation after the infection has been cleared.

Rottier et al. (2023) [39] highlighted the role of rifampicin and fluoroquinolones as essential components of PJI treatment regimens. These antibiotics are particularly effective in penetrating biofilms and inhibiting bacterial growth within these protective layers. Rifampicin is highlighted for its potent activity against *Staphylococcus* species, especially when used in combination with other agents like fluoroquinolones to prevent the development of resistance. The review advocates for ongoing research into novel antimicrobial agents and strategies to combat biofilm-associated infections, which remain a major barrier to successful PJI management.

Schindler et al. (2023) [40] reviewed 19 individual studies that explored the use of emerging diagnostic markers beyond traditional indicators like CRP and ESR. One of the key findings of this review is the potential role of calprotectin as a highly sensitive and specific biomarker for detecting PJIs. Calprotectin is an inflammatory protein released by neutrophils, and its elevated levels in synovial fluid have shown a strong correlation with PJIs. The review demonstrated that calprotectin offers both high sensitivity and specificity, making it a promising tool for early diagnosis, which is critical for timely intervention and better clinical outcomes.

Zhao et al. (2024) [41] included data from 8,711 revision cases across 40 studies, making it one of the most extensive analyses to date on this topic. The study found no significant difference in reinfection or reoperation rates between single-stage and two-stage revision

procedures. Despite the common perception that two-stage revisions provide a more definitive solution to chronic PJIs, particularly in cases with biofilm-producing organisms, the study's findings suggest that single-stage revisions can offer comparable outcomes under certain circumstances. This conclusion has important implications for clinical decision-making, particularly in patients where minimizing surgical interventions is a priority due to comorbidities or other risk factors.

Rodriguez-Merchan et al. (2022) [42] conducted a narrative review focused on patient-related, surgical, and postoperative factors that influence the likelihood of developing PJIs, offering insights into prevention and management strategies. The review identified male gender, diabetes, and obesity as the most significant patient-related risk factors for PJIs following TKA. Male patients, particularly those with comorbid conditions such as diabetes and elevated BMI, were found to have a higher incidence of infections compared to female patients. The metabolic and immunological changes associated with diabetes and obesity were highlighted as contributing factors that impair wound healing and increase susceptibility to infection. Surgical factors also played a key role, with longer operative times, complex procedures, and the use of cemented prostheses being linked to increased infection rates.

Tsikopoulos et al. (2023) [43] synthesized findings from multiple studies to provide a comprehensive overview of the most reliable markers for diagnosing PJIs, which are critical in guiding timely and appropriate treatment. The review highlighted that *Staphylococcus aureus* and *Staphylococcus epidermidis* were the most commonly isolated pathogens in PJIs, particularly in infections related to biofilm formation on prosthetic materials. *S. aureus* was often associated with acute, more aggressive infections, while *S. epidermidis*, a coagulase-negative *Staphylococcus*, was linked to chronic, low-grade infections that are harder to detect and treat due to their biofilm-forming capabilities.

Almeida et al. (2021) [44] analyzed 75 articles on the risk factors associated with perioperative wound dehiscence (PWD) in total joint arthroplasty (TJA) patients. The review focused on patient-related, pharmacological, and surgical factors that contribute to an increased risk of PWD, which is a common postoperative complication that can lead to PJIs. The review identified several key patient-related risk factors, including smoking, obesity, and anemia. Smoking was strongly linked to PWD due to its adverse effects on wound healing and tissue oxygenation. Obesity, reflected by a high BMI, was another significant risk factor, as excessive adipose tissue complicates wound closure and healing.

Anemia, particularly in the preoperative period, was associated with impaired wound healing and increased susceptibility to wound breakdown.

Dobson and Reed (2020) [45] analyzed 119 articles focused on strategies to reduce infections in primary THA and TKA. The review evaluated operating room practices, microbiological factors, and surgical techniques that influence infection rates in these procedures. The review identified MSSA as the most common pathogen associated with infections in primary THA and TKA. MSSA's prevalence underscores the importance of preoperative screening and decolonization protocols to reduce infection risk. It was emphasized that targeted antibiotic prophylaxis is essential to prevent postoperative infections caused by this pathogen. Operating room factors, particularly the use of perioperative blood transfusions, were also associated with an increased risk of infections. Transfusions can have immunosuppressive effects, making patients more susceptible to infections. Surgical techniques that prolong operative time or increase tissue trauma were similarly linked to higher infection rates, highlighting the need for optimizing surgical protocols.

Alamanda and Springer (2018) [46] highlighted the critical role that patient-related and perioperative factors play in the development of PJIs, with an emphasis on those that can be altered to reduce infection risk. The review identified obesity, diabetes, smoking, and poor oral health as key modifiable risk factors. Obesity was found to be a major contributor to increased PJI rates due to its impact on wound healing and immune function. Patients with a higher BMI face a greater risk of surgical site infections, and this risk grows proportionally with the severity of obesity. Diabetes, particularly in cases where blood glucose levels are not well-controlled, was another major factor, given its adverse effects on immune system efficiency and tissue repair. Smoking, due to its impact on tissue oxygenation and immune response, was also strongly associated with an increased risk of infections.

DISCUSSION

FINDINGS SUMMARY

This narrative review has compiled evidence from 23 studies and 11 reviews reporting various aspects of PJIs, with a focus on microbial, biomechanical, and patient-related risk factors, as well as treatment outcomes. The predominance of Gram-positive bacteria such as *Staphylococcus aureus* in PJIs is consistent across multiple studies [39], while *Candida* species have emerged as significant pathogens in more com-

plex, polymicrobial infections [14]. Individual factors, including high BMI, diabetes, and advanced age, have been repeatedly identified as critical risk factors for PJIs, which complicates treatment strategies [17, 18]total Hip arthroplasty (THA). Additionally, several studies support the notion that two-stage revision surgeries provide better long-term outcomes in terms of infection-free survival, particularly in chronic or biofilm-associated infections [33, 34]management of recurrent infection after a two-stage exchange remains debated and the outcome of a repeat two-stage procedure is unclear. This study investigates the success rates of repeat two-stage exchange arthroplasty and analyzes possible risk factors for failure.

Materials and methods

We retrospectively identified 55 patients (23 hips, 32 knees). Diagnostic advancements, especially novel biomarkers like calprotectin, offer promising potential for improving the early detection of PJIs [40]

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KNOWLEDGE GAPS

Despite significant advancements, there are notable gaps in the understanding and management of PJIs. One such gap involves the variability in diagnostic criteria across institutions, particularly in the use of biomarkers like calprotectin or alpha-defensin. While these biomarkers show promise, their clinical utility requires further validation in large, multicenter trials to establish consistent cut-off values and integration into diagnostic protocols [40]the aim of this systematic review is to identify and evaluate the effectiveness of novel biomarkers for the diagnosis of PJI.

METHODS: We searched the MEDLINE, EMBASE, PubMed, and Cochrane Library databases from January 1, 2018, to September 30, 2022, using the search terms "periprosthetic joint infection," "prosthetic joint infection," or "periprosthetic infection" as the diagnosis of interest and the target index, combined with the term "marker." We excluded articles that mentioned established biomarkers such as CRP, ESR, Interleukin 6, Alpha defensin, PCT (procalcitonin). Another critical gap is the lack of consensus on the best surgical approach for treating PJIs. While two-stage revisions are widely considered the gold standard, the recent findings [41] question this, showing no significant difference in outcomes between one-stage and two-stage revisions in

select cases. Further research is needed to determine the patient populations and infection profiles that may benefit from a one-stage approach. Additionally, more research is necessary on how to optimize antimicrobial therapy in the context of biofilm-associated infections, as many current treatments remain inadequate against biofilm-producing organisms.

FUTURE DIRECTIONS

Future research should focus on closing the knowledge gaps identified in this review. First, efforts should be made to establish standardized diagnostic protocols that incorporate novel biomarkers alongside traditional methods like CRP and ESR. This will ensure earlier and more accurate diagnoses, which are critical for improving patient outcomes. Additionally, prospective randomized trials are needed to further evaluate the comparative efficacy of one-stage versus two-stage revision surgeries, especially in cases involving low-virulence organisms or well-characterized infections [41]. Another important avenue for future research is the development of biofilm-targeted therapies. Studies should explore novel antimicrobial agents or delivery systems that can effectively disrupt biofilms on prosthetic surfaces. Finally, exploring the role of patient optimization strategies, such as preoperative weight management and glycemic control, in reducing PJI risk in high-BMI or diabetic patients, would be beneficial [21, 37].

CONCLUSIONS

This narrative review highlights the multifaceted nature of periprosthetic joint infections (PJIs), which remain a major complication in arthroplasty procedures, particularly in high-risk populations such as those with obesity, diabetes, or chronic pulmonary conditions. The predominance of Gram-positive bacteria, particularly *Staphylococcus aureus*, remains a constant, though the increasing emergence of *Candida* species in polymicrobial infections adds to the complexity of management. Advances in diagnostic biomarkers like calprotectin and novel treatment modalities, including biofilm-active antibiotics, represent promising developments but require further clinical validation. Importantly, this review underscores the ongoing debate regarding one-stage versus two-stage revisions for PJIs. While two-stage procedures are still considered the gold standard for chronic or biofilm-associated infections, some studies suggest that single-stage revisions may offer comparable outcomes in selected cases, challenging traditional surgical paradigms. The integration of standardized

diagnostic protocols, biofilm-targeted therapies, and a more nuanced understanding of surgical interventions will be crucial for improving outcomes in patients suffering from PJIs. Additionally, optimizing patient health through preoperative interventions such as weight

management and diabetes control should be prioritized to minimize infection risks in vulnerable populations. Continued research into these areas will be essential for developing more effective and tailored strategies for PJI prevention and treatment

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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