Journal of Orthopaedic Surgery and Research

REVIEW

Open Access

Periprosthetic joint infection after arthroplasty: advances and future prospects

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Abstract

Objective To comprehensively analyze the prevention, diagnosis and management strategies of periprosthetic joint infections(PJIs), provide new ideas for overcoming PJI, and provide references for clinicians.

Methods By synthesizing the latest research results at home and abroad, this study deeply analyzed the multidimensional prevention strategies, diagnostic criteria and technological advances, and treatment management strategies for PJI.

Results The management of PJI remains a significant challenge in orthopedic surgery, which warrants focused attention. The prevention of PJI holds paramount priority and should be integrated throughout the perioperative period. Although diagnostic criteria for PJI have undergone multiple updates, the 2011 MSIS criteria remain the most widely adopted, requiring comprehensive evaluation of laboratory, pathological, and imaging examinations for diagnosis. PJI treatment necessitates combined antibiotic and surgical interventions. Antibiotic therapy includes empirical treatment after diagnosis, targeted therapy following pathogen identification, and suppressive antibiotic therapy(SAT) for non-surgical candidates. Surgical options comprise debridement, antibiotics, and implant retention(DAIR), one-stage/two-stage revision, and salvage procedures.

Conclusion Implementation of standardized infection prevention protocols, rational antibiotic use, surgical technical innovations, and advancements in biomaterials have contributed to a reduction in PJI incidence. However, the spread of bacterial resistance and multidrug-resistant organisms in healthcare settings pose new challenges for PJI prevention and treatment. In the future, the research and development of new antimicrobial materials, the innovation of biofilm control technology and the application of precision medicine are expected to further reduce the incidence of PJI, improve the quality of life of patients, and promote a breakthrough in the field of arthroplasty regarding this issue.

Keywords Total joint arthroplasty, Periprosthetic joint infection, Revision surgery, Preventive strategies, Therapeutic advances

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Introduction

Arthroplasty, especially Total Hip Arthroplasty(THA) and Total Knee Arthroplasty(TKA), has become an effective means of treating end-stage joint diseases since the middle of the 20th century. It can significantly relieve pain, improve joint function, and enhance the quality of life of patients [1]. As a serious complication of arthroplasty, PJI greatly affects the surgical outcome and brings physical and mental pain as well as a heavy economic burden to patients. According to statistics, the incidence of PJI after initial hip and knee replacement is 1–3% [2, 3], and the re-infection rate in revision surgery is as high as 16% [4–6]. In recent years, with the continuous increase in the volume of arthroplasty, the number of PJI cases is expected to rise. An epidemiologic study in the United States predicted [7] that by 2030, the number of revision hip cases would increase by 68%-176%, and the number of revision knee cases would increase by 72%-170%. Therefore, the prevention and treatment of PJI have become an important topic in the field of orthopedics. Although many different recommendations for the management of PJI have been published, no consensus has been reached in many aspects; most studies have provided fragmented insights and lacked comprehensive and in-depth exploration [8–10]. In contrast, this study comprehensively analyzes the prevention, diagnosis, and treatment strategies of PJI based on the latest domestic and international studies, offering comprehensive and forward-looking strategies for PJI management. In view of the challenges of increased bacterial resistance and difficult biofilm removal in the current treatment of PJI, we provide new ideas and directions to overcome PJI. Our aim is to provide clinicians with a comprehensive and practical reference to promote the development of clinical practice in this field.

Prevention strategies for PJI

PJI is a devastating complication for both patients and physicians. All patients should adopt prevention strategies to reduce the risk of PJI. By implementing multi-dimensional strategies covering preoperative, intraoperative, and postoperative aspects, we can effectively lower the infection risk and revision rate, save healthcare resources, remarkably improve patients' prognosis and quality of life, and even mitigate the risk of medical disputes(Table 1).

Table 1 Prevention strategies for PJI

Prevention stages	Prevention strategies	Specific measures
Preoperative prevention	Risk factors screening and health optimization	Inflammatory markers[11.12], Nutritional status[13-18], Blood glucose[19-23], Morbid obesity[24], Smoking[25-28]
	Skin preparation	Hair removal[29], Preoperative decolonization[30-35]
	Perioperative antibiotics	Preoperative antibiotic administration[36-39]
	Operating room environment	Laminar flow system[40-45]
Intraoperative prevention	Aseptic principles	Hand hygiene[46], Double gloving and replace them regularly[47], Control the flow of operating room personnel[48.49]
	Minimally invasive techniques	Reduce blood transfusion events[50-59]（Reduction of surgical incisions[50.51], Tranexamic acid[54.55], Tourniquet[56.57], Shorten the operation time[58.59])
	Soft tissue protection	Avoid touching soft tissues with hands and contaminated gloves, Reduce soft tissue traction, Control the frequency and intensity of electrocautery use[60]
	Implants and material-related preventive	Select antibacterial-coated implants[61.62], Antibiotic-impregnated bone cement[63-65], Antibiotic-impregnated allograft[66]
	Flushing solutions	Povidone-iodine solution[67-69], 3% hydrogen peroxide soluton[70], 3% acetic acid solution[71]
	Management of surgical incisions	Layered closure and continuous suturing[72-76], Antimicrobial sutures[73.79], Close the wound with sutures[72.73], Barbed suture[72.73]
	Drainage	Drainage tubes[81-88]
Postoperative prevention	Wound care	Silver-impregnated occlusive dressings[89-91]
	Extended antibiotic prophylaxis	Extended oral antibiotics[92-101]

Preoperative prevention strategies

Preoperative risk factor screening and health optimization

Orthopedic surgeons should promptly identify patients' risk factors before surgery including inflammatory markers, nutritional status, diabetes, morbid obesity, and smoking.

Elevated preoperative serum inflammatory markers have been associated with the incidence of surgical site infections(SSIs)/PJIs following primary THA. For instance, C-reactive protein(CRP) > 1.0 mg/dL and erythrocyte sedimentation rate(ESR) > 20 mm/h are recognized as risk factors for SSIs and PJIs [11]. Similarly, Xu et al. reported that patients with elevated preoperative ESR and CRP exhibited a higher probability of developing TKA PJI compared with the normal group [12]. Therefore, timely intervention is advised, and measures such as using antimicrobial implants or antibiotic-loaded bone cement stems should be considered to reduce infection risk. Malnutrition has been identified as a potential risk factor for PJI, with associations to adverse outcomes in total joint arthroplasty(TJA) [13]. Adequate nutritional status serves as the foundation of the immune system. Preoperative systematic assessment of patients' nutritional status, including hemoglobin [14], serum albumin [15], transferrin [16], BMI [17], and vitamin D [18], and implementation of targeted nutritional interventions for malnourished patients are crucial for reducing the postoperative infection rate in TJA. Diabetes has been identified as an important risk factor for postoperative complications after TJA. HbA1c is used to reflect average blood glucose control over the preceding 2–3 months, with a clinical target of HbA1c ≤ 7.0% widely adopted. This standard has been shown to significantly reduce postoperative complications and optimize outcomes [19]. Equally critical is strict perioperative glycemic control, as stable euglycemia has been associated with a reduced risk of postoperative infection [20, 21]. Recent investigations have identified fructosamine as an effective predictor of PJI after TJA, with levels > 293μmol/L significantly increasing PJI risk [22, 23]. Though albumin-corrected fructosamine did not show any additional benefits, further validation of its clinical utility is needed [23]. For morbidly obese(BMI > 40 kg/m^2) patients, preoperative weight loss is recommended. Studies have demonstrated that morbid obesity significantly raises the risk of perioperative complications. It can cause poor wound healing, a substantial increase in the infection probability, and a higher risk of prosthesis loosening, dislocation, and revision, all of which severely impact the surgical outcome and patient prognosis [24]. Moreover, numerous studies have shown [25–28] that preoperative smoking cessation can effectively reduce the risk of TJA postoperative complications, including PJI.

Preoperative skin preparation

Although hair removal at the surgical area constitutes a routine component of preoperative preparation, existing evidence has shown no significant effect in reducing infection risk. When hair removal is necessary, a higher infection rate is exhibited by patients using razors compared with those using scissors, suggesting that mechanical damage may enhance bacterial skin colonization [29].

Staphylococcus aureus is identified as the predominant pathogen in PJI, with a nasal carriage rate of 25–30% [30]. Nasal colonization is observed even in non-high-risk patients. Universal decolonization for all TJA patients is supported by evidence, as it prevents missed diagnoses, reduces PJI incidence, and demonstrates cost-effectiveness [31]. The standard decolonization protocol is composed of intranasal mupirocin and chlorhexidine(CHG) bathing for 5 days preoperatively. This approach has been proven effective across surgical specialties, leading to a 79% reduction in deep surgical site infections [32]. Skin bacterial load is further decreased by additional CHG bathing on the night before and morning of surgery [33]. Compared with povidone-iodine, chlorhexidine-alcohol disinfection of the surgical area before operation has been shown to significantly reduce the overall infection rate, particularly the deep incision infection rate [34]. Additionally, nasal povidone-iodine solution serves as an alternative decontamination method [35].

Perioperative antibiotics

Perioperative antibiotic prophylaxis is a core strategy for preventing PJI. Timing of prophylactic administration is critical. Guidelines recommend a single intravenous dose of broad-spectrum antibiotics within 1 h before surgical incision, typically at anesthesia induction, with prophylactic antimicrobials discontinued within 24 h post-surgery [36]. First-generation cephalosporins(e.g., cefazolin) are widely used in orthopedic surgery owing to their potent anti-*staphylococcal* activity, good and rapid bone, soft tissue, and muscle concentrations [37]. For patients at high risk of methicillin-resistant *Staphylococcus aureus*(MRSA) infection, dual prophylaxis with cephalosporins and vancomycin is advised [38]. While a single preoperative dose suffices for most cases, repeated administration during surgery is required to maintain effective blood concentrations when surgical duration exceeds two drug half-lives, blood loss exceeds 1,500 mL, or extensive burn injury is present [39].

Operating room environment

The management of the operating room environment is a crucial aspect of infection prevention. Laminar flow systems are designed to offer a highly clean and sterile setting for surgical procedures. Early research indicated that these systems might be able to reduce the risk of

infection [40, 41]. However, subsequent large-scale studies have revealed that, when comprehensive infection control measures are in place, laminar flow systems do not exhibit significant advantages [42–45]. In fact, there is even evidence suggesting a correlation between their use and early postoperative infections [44]. Currently, insufficient data are available to support the routine use of laminar flow systems. Their actual effectiveness may be affected by the multifactorial pathogenic mechanism of PJI, and further research is needed to confirm their value.

Intraoperative prevention strategies

Aseptic principles

Strictly adhering to aseptic procedures is the cornerstone of intraoperative infection prevention and control. Research has demonstrated that the hand hygiene of surgical staff is directly associated with the postoperative infection rate [46]. All surgical team members must don sterile surgical gowns and double-layered gloves, and gloves should be replaced regularly based on the frequency of the surgical procedure [47]. Moreover, the flow of personnel in the operating room should be tightly regulated to minimize the presence of non-essential individuals. Some studies have indicated that there is a positive correlation between intraoperative personnel density and the number of environmental bacteria [48, 49].

Application of minimally invasive techniques

Minimally invasive surgery can mitigate the risk of intraoperative bacterial infection by reducing the size of surgical incisions, decreasing blood loss, and shortening tissue exposure time [50, 51].

Studies have confirmed that allogeneic blood transfusion and hematoma formation are significant risk factors for the elevated incidence of surgical site infections in TJA [52, 53]. Conversely, the intravenous or topical administration of tranexamic acid effectively decreases perioperative blood loss and allogeneic transfusion, thereby reducing the overall infection rate [54, 55]. The use of an intraoperative tourniquet is effective in reducing intraoperative bleeding, providing a clear surgical field and shortening the operation duration. However, it may increase the risk of complications such as thrombosis, quadriceps weakness, and delayed recovery of knee function [56]. Some researchers propose shortening the tourniquet application time to minimize postoperative complications. A meta-analysis by Zan et al. [57] indicated that releasing the tourniquet before wound closure increases total perioperative blood loss but may decrease the risk of various complications. The use of tourniquets remains controversial, and further studies are needed for conclusive evidence. In addition, operative duration is recognized as a controllable risk factor. Studies [58] have demonstrated that each 15-minute increment in surgical time is associated with a 9% increase in infection risk. Similarly, Wang et al. [59] reported that each 20-minute prolongation of surgical duration in primary TJA was associated with a nearly 25% increase in the risk of PJI. These findings suggest that optimizing operative efficiency may reduce the potential for infection.

Soft tissue protection

In arthroplasty, protecting soft tissues plays a crucial role in preventing surgical site infections. During the procedure, hands and contaminated gloves should not come into contact with soft tissues; instead, surgical instruments should be used for precise manipulation. The incision size must be carefully calibrated. An incision that is too small can impede surgical maneuvers, while an overly large one increases the risk of tissue damage and infection [50, 51].

Additionally, unnecessary retraction should be minimized to reduce tissue trauma. Studies [60] have demonstrated that excessive electrocautery can compromise local blood flow and tissue repair capabilities, thereby increasing the risk of infection. Therefore, the frequency and intensity of electrocautery applications need to be strictly regulated.

Implants and material-related preventive measures

Antimicrobial-coated bone implants represent an effective strategy for PJI prevention. Silver ion(Ag^+) coatings exert antibacterial effects by releasing ions that disrupt bacterial membranes and inhibit metabolism. These coatings have been shown in studies [61, 62] to reduce PJI risk, attributed to their broad-spectrum activity and biocompatibility. Antibiotic-impregnated bone cement has served as a valuable tool in preventing and treating orthopedic infections for over four decades [63]. Two recent meta-analyses [64, 65] demonstrate its efficacy in reducing deep infection rates after primary TKA. Synergistic combination with gentamicin further augments its therapeutic efficacy.

Additionally, antibiotic-impregnated allograft bone, which provides sustained local drug release(maintaining high concentrations), thus, is commonly used in revision surgeries with elevated infection risk [66].

Flushing solutions

The use of a flushing solution before closing the incision is an important preventive measure. Currently, povidone-iodine solution is the most commonly used clinical solution. Typically, about 20 mL of 10% povidone-iodine is diluted in 500–1000 mL of saline. During the operation, the joint is soaked in this solution for 3 min, and then thoroughly rinsed. As proven by several clinical studies [67–69], through the oxidation of iodine, it can disrupt

the bacterial structure and significantly reduce the incidence of PJI.

The 3% hydrogen peroxide solution can effectively kill bacteria, viruses, and fungi. It does so by oxidatively damaging biomolecules, disrupting the cell-membrane structure, and interfering with cell metabolism. This solution can effectively reduce the number of microorganisms at the surgical site [70]. However, its preventive efficacy in TJA remains unclear, and further research is needed to verify its effect.

The 3% acetic acid solution exerts a broad-spectrum bactericidal effect by lowering the pH value of bacterial cells. Some studies have shown that its success rate in preventing PJI can reach up to 87% [71]. Nevertheless, more high-quality studies are required to confirm its clinical value in PJI prevention.

Management of surgical incisions

The closure of incisions after TJA remains critical. Ideal suturing emphasizes layered closure from deep to superficial tissues to facilitate wound healing and reduce complication risks [72, 73]. Current studies recommend continuous suturing with barbed sutures, eliminating the need for knotting, especially for deep fascial layers, to achieve efficient tissue approximation, uniform tension distribution, and watertight sealing, thereby preventing dead space formation and minimizing wound complications [74–76]. A semi-flexed position is advised during knee closure to optimize mobility, with emphasis on watertight closure of the deep fascial layer(joint capsule) [75]. For hip joint closure, stability serves as the core principle, requiring anatomical reduction of deep structures including the joint capsule and external rotators [77].

The choice of suture materials is also associated with wound complications. Studies have shown that bacteria adhere 5–8 times more readily to braided sutures than to monofilament sutures(e.g., nylon) [78]. An international consensus has recently indicated that sutures with triclosan antibacterial coatings can reduce the risk of SSI in TJA [73, 79]. Research has demonstrated a significantly higher risk of wound infection when staples are used for incision closure after TJA [80]. This consensus notes that in THA, stapling techniques carry a higher risk of superficial SSI compared with suture techniques, although they offer shorter closure time; skin adhesives show no significant difference in wound complication rates compared with other skin closure methods [72]. In TKA, wound complication rates are comparable among staples, subcuticular sutures, and skin adhesives [73]. Additionally, barbed sutures significantly reduce operative time and cost, and have been proven to reduce wound complications in TKA. However, current evidence remains inconclusive regarding the advantages of barbed sutures in reducing wound complication risk after THA [72, 73].

Drainage tubes

In the postoperative management of arthroplasty, traditional practice [81, 82] has long advocated indwelling drainage tubes as a routine strategy to prevent hematoma formation and reduce dressing change frequency. Hematoma formation was previously associated with increased local tissue tension, which not only limits early joint mobility and delays wound healing but also creates a suitable microenvironment for bacterial growth, thereby increasing the risk of infection. However, modern evidence-based research has challenged this convention. Multiple studies have shown that [83–85] postoperative drainage in arthroplasty provides no additional clinical benefit. Conversely, it may increase the incidence of postoperative blood transfusions and serve as a pathway for bacterial invasion, significantly raising the risk of catheter-related infections.

Currently, there is insufficient evidence to support or oppose the routine use of closed drainage in TJA. Until further high-quality multicenter studies are published, decisions on drainage should be personalized to patient-specific factors rather than adopting a simplistic "use or discard" approach [86]. For patients with substantial intraoperative blood loss during TJA, consideration may be given to indwelling a negative-pressure drainage tube, combined with intra-articular injection of tranexamic acid, application of compressive bandaging after skin closure, and temporary clamping of the drain for the first 3 h postoperatively [87]. Additionally, strict adherence to the principle of "early removal" (≤ 24 h) [88] is recommended to balance the dual goals of hematoma prevention and infection control.

Postoperative prevention strategies

Wound care

Postoperative wound management remains of critical part of prevention strategies, and it is important to emphasize avoiding wound care within the first 48 h. Maintaining the wound in a sterile condition during this period is critical, alongside the use of an occlusive dressing. Occlusive dressings facilitate wound healing by maintaining a moist microenvironment, minimizing exudate accumulation, and inhibiting microbial colonization, thereby providing wound protection [89]. Recent investigations have demonstrated that occlusive dressings impregnated with silver ions achieve dual objectives of wound care and infection prophylaxis. These dressings are directly applied and secured during the surgical procedure, eliminating the need for manipulation in the early postoperative period. The initial dressing change is typically performed seven days postoperatively. By reducing

dressing change frequency, extending occlusion duration, and harnessing the antimicrobial activity of silver ions, an optimal balance between infection prevention and wound healing is established, leading to a fourfold reduction in acute PJI [90]. Consistently, Toppo et al. [91] have shown that silver-impregnated occlusive dressings represent a cost-effective strategy for preventing infections following TJA.

Extended antibiotic prophylaxis(EAP)

Studies by Christensen [92] and Tan [93] et al. have indicated comparable efficacy between single-dose and 24-hour antibiotic regimens in preventing PJI after primary TJA. Similarly, a recent meta-analysis of 9 studies involving 295,654 patients has shown that single-dose prophylactic antibiotic regimen may be preferable for reducing PJI incidence in primary TJA [94].

For aseptic revision TJA, EAP has been shown to significantly reduce infection rates in several studies [95, 96]. A meta-analysis including 18 studies and 19,153 patients revealed that extended prophylactic antibiotics decreased PJI incidence after aseptic revision TKA, but no significant difference was observed in aseptic revision THA [97]. Mohiuddin et al. suggested that EAP may be warranted after aseptic revision THA to prevent catastrophic PJI, as existing evidence does not refute the efficacy of EAP [95]. Collectively, EAP may be considered for aseptic revision TKA, whereas its use in THA warrants cautious evaluation. However, the limited quality of current studies necessitates high-quality prospective trials to confirm these findings.

For high-risk TJA patients, some studies have proposed that a 7-day postoperative oral antibiotic regimen after discharge can significantly reduce infection rates [98]. Conversely, DeFrancesco et al. [99] highlighted that extended antibiotic use may increase risks of resistance and adverse events, recommending careful benefit-risk assessment given the limited evidence. Current studies remain inconsistent [96, 100, 101], and whether high-risk populations should adopt EAP requires high-quality prospective studies to clarify benefits and risks.

Diagnosis of PJI

The evolution of the diagnostic criteria for PJI

As a mature technique, TJA has significantly enhanced the quality of life for numerous patients. However, PJI, a severe complication, remains a persistent challenge in the field of TJA. Although the diagnostic criteria for PJI have been revised multiple times since their initial development in 2011, the current criteria still harbor certain limitations(Table 2). Further exploration is required to improve the diagnostic accuracy of PJI in the future.

The first set of PJI diagnostic criteria was developed by the Musculoskeletal Infection Society(MSIS) in 2011 [102] and is currently the most widely adopted. The primary criteria include the presence of a sinus tract communicating with the prosthesis and the isolation of the same pathogen from two specimens. Secondary criteria involve elevated ESR and CRP levels, increased synovial leukocyte counts, a higher percentage of synovial neutrophils, articular sepsis, isolation of microorganisms in periprosthetic tissue or fluid cultures, and the observation of more than five neutrophils in each of five fields of view at 400× magnification during histologic analysis of periprosthetic tissues. Patients meeting fewer than four secondary criteria suggest a possible PJI.

The first International Consensus Meeting on Periprosthetic Joint Infection(ICM) in 2013 further refined the MSIS diagnostic criteria, forming the "Philadelphia Consensus" [103]. This consensus added joint fluid leukocyte esterase(LE) testing to the secondary criteria, removed joint sepsis as an indicator, and defined a threshold for chronic PJI based on the time since the most recent surgery(>6 weeks). It emphasized applying the same diagnostic criteria to both TKA and THA. Nevertheless, this consensus was established based on expert opinions and lacked large-scale clinical validation.

The PJI diagnostic criteria were updated again at the second ICM in 2018 [104]. The primary criteria remained similar to those of the 2013 consensus. For the secondary criteria, a more detailed categorization was made according to different preoperative and intraoperative conditions, and a scoring system was introduced to quantify various indicators, making the diagnosis more accurate and objective. Meanwhile, this version of the consensus highlighted the role of serum D-dimer in PJI diagnosis and, for the first time, included joint fluid alpha-defensin as a diagnostic indicator.

In 2021, with the support of the MSIS, the European Bone and Joint Infection Society(EBJIS) updated the definition of PJI [105], proposing a three-level definition principle: "infected unlikely", "infected likely", and "infected confirmed". This change better aligns with clinical reality and helps physicians more accurately assess patients' infection status. In terms of diagnostic criteria, the importance of clinical manifestations and nuclear imaging in diagnosis was emphasized. A detailed evaluation of clinical manifestations can assist doctors in detecting subtle signs of latent infections, while nuclear imaging provides more intuitive evidence, which has important auxiliary value.

Advances in PJI diagnostic techniques

Accurate diagnosis of PJI directly affects treatment decisions and prognosis. Although traditional diagnostic methods are still the cornerstone, they have limitations when it comes to early infections, low-virulence pathogens, and complex cases. In recent years, with the

Table 2 The evolution of the diagnostic criteria for PJI

Version / Examination	2011 MSIS Criteria[102]	2013 ICM Criteria[103]	2018 ICM Criteria[104]	2021 EBJIS Criteria[105]
Clinical indicators	Sinus tract (major); Puruce (minor).	Sinus tract(major); Purulence(removed).	Sinus tract (major); Purulence (minor,3 points).	Sinus tract (infection confirmed); Purulence (infection likely); Periprosthetic fracture nonunion (infection likely); Recent history of fever (infection likely); Secretions around the prosthesis (infection likely).
Peripheral blood serological	CRP and ESR：↑（minor）	CRP：＞10mg/L（chronic） ESR：＞30mm/h（chronic）（minor）	CRP>10 mg/L (preoperative,minor,2 points); D-dimer>860ng/mL(preoperative,minor,2points); ESR > 30 mm/h (preoperative,minor,1 point).	CRP > 10 mg/L (infection likely）
Synovial fluid cytological	WBC: ↑ (minor); PMN%: ↑(minor).	WBC>3000/μL (chronic) (minor); PMN%>80% (chronc) (minor).	WBC>3000/μL (preoperative,minor,3 points); PMN%>90% (preoperative,minor,2 points).	WBC>1500/μL (infection likely); >3000/μL (infection confirmed), PMN%>65% (infection likely); >80% (infection confirmed).
Synovial fluid serological	/	LE: (++) (minor)	α-defensin:positive(preoperative,minor,3points); LE: (++) (preoperative,minor,3 points).	α-defensin: positive (infection confirmed)
Pathogen detection	Periprosthetic tissue or synovial fluid culture: ≥ 2 positive results (major); 1 positive result (minor).	Periprosthetic tissue or synovial fluid culture: ≥ 2 positive results (major); 1 positive result (minor).	Periprosthetic tissue or synovial fluid culture: ≥2 positive results (postoperative,major); 1 positive result (postoperative,minor,2 points).	Periprosthetic tissue or synovial fluid culture: ≥ 2 positive results (infection confirmed); 1 positive result (infection likely. If the preoperative puncture and intraoperative tissue culture yield the same microorganism, it can be regarded as two positive confirmatory samples), sonication fluid>1CFU/mL(infection likely); > 50CFU/mL(infction confirmed).
Histopathological	> 5 neutrophils in each of 5 high-power fields (minor)	> 5 neutrophils in each of 5 high-power fields (minor)	>5 neutrophils in each of 5 high-power fields (postoperative, minor, 3 points)	> 5 neutrophils in each of 5 high-power fields(infection confirmed); > 5 neutrophils in 1 high-power field (infection likely), visible microorganisms (infection confirmed).
Nuclear imaging	/	/	/	Radiological signs of loosening within 5 years after, implantation (infection likely), positive WBC scintigraphy (infection likely).
Diagnostic criteria	≥1 major criterion; or ≥4 minor criteria are met. Otherwise, it suggests the possible presence of PJI.	≥1 major criterion; or ≥3 minor criteria are met.	Preoperative tests: (≥6 points for diagnosis, 2-5 points require further surgical exploration, 0-1 point rules out infection); Postoperative tests (sum of preoperative and postoperative test scores):≥6 points for diagnosis, 4-5 points require molecular biology testing, ≤3 points rule out infection. CRP and D-dimer, WBC and LE are not scored repeatedly due to high collinearity.	/

application of emerging technologies and indicators, the bottleneck of traditional methods is being gradually overcome, significantly optimizing the diagnostic efficacy and providing key support for individualized patient treatment(Table 3).

Laboratory tests

Serum biomarkers CRP, ESR, and white blood cell count(WBC) are fundamental serum markers for diagnosing PJI. Owing to their convenience and cost-effectiveness, they are frequently used as initial screening tools. However, their sensitivity and specificity are limited. Their elevation can occur in postoperative non-infectious

Table 3 The diagnostic techniques for PJI

Categories	Tools	Specific indicators/techniques
Laboratory tests	Serum biomarkers	Fundamental markers[106-108](CRP, ESR, WBC), IL-6[109.110.112.113], PCT[111.114.115], HPB[116.117], D-dimer[118.119.123.124], FIB[120-122.125], Blood cell ratio[126-128]
	Joint fluid biomarkers	Fundamental markers[102.105.129-131](WBC, PMN%, IL-6, CRP), LE[105.132.133], AD[123.134.135], Calreticulin[136-141], D-lactate[142-144], Presepsin[145], LCN2[146], NGAL[147], cfDNA[148], IL-1β[149]
	Microbial culture	Molecular biology techniques[105.152-156](PCR, mNGS, FISH), Ultrasound technology[105.157-161]
Pathological examination	Histopathological examination	Preoperative biopsy[163.164], Intraoperative frozen section biopsy[165], Postoperative histopathologic examination[164]
Imageological examination	Imaging technology	X-ray[166], MRI and MARS-MRI[167-170], NM imaging technology[105.171-174](Three-phase bone scintigraphy, Leukocyte scintigraphy, FDG - PET), Color ultrasound of the inguinal lymph nodes[175]

inflammation or complications, and false negatives or low values may arise with low-virulence pathogens or chronic PJI [106–108]. Therefore, these indicators should be interpreted with caution.

In recent years, interleukin-6(IL-6) [109, 110] and procalcitonin(PCT) [111] have gained increasing attention in PJI diagnosis. Elgeidl et al. [112] found that IL-6 outperforms traditional markers in diagnosing PJI, and the combination of IL-6 and CRP significantly improves sensitivity and specificity. Similarly, Zhang et al. [113] found that serum IL-6 demonstrated excellent diagnostic performance in both acute and chronic PJI. As a promising auxiliary diagnostic indicator, it requires further validation in larger cohorts. PCT is highly specific for bacterial infections, rendering it particularly valuable in the assessment of systemic infections [114]. However, its utility is limited in cases of localized, low-virulence PJI; a recent study has demonstrated [115] that PCT is not suitable as a serum biomarker for the diagnosis of PJI, although further validation is needed.

Recent studies [116, 117] have proposed that azurocidin 1(AZU1), also known as heparin-binding protein(HPB), is a new biomarker for PJI diagnosis. However, only a few studies have been conducted, and more research is required for confirmation. In addition, D-dimer [118, 119] and fibrinogen(FIB) [120–122] are commonly used as auxiliary tests. D-dimer was included as a secondary diagnostic criterion in the 2018 ICM. However, its results are easily influenced by factors such as thrombus and trauma, and several studies [123, 124] suggest that its diagnostic value may be limited. In contrast, FIB has demonstrated better diagnostic value [125]. Therefore, the application of serum D-dimer as a diagnostic marker for PJI needs further validation through larger-scale clinical studies.

In recent years, blood cell ratios such as the neutrophil-to-lymphocyte ratio(NLR), platelet-to-mean platelet volume ratio(PVR), platelet-to-albumin ratio(PAR), and C-reactive protein-to-albumin ratio(CAR) have been identified as potential infection markers. However, their validity requires confirmation through additional studies [126–128].

Joint fluid biomarkers Joint fluid testing can directly reflect the local infection condition of the joints and plays a pivotal role in the accurate diagnosis of PJI. Besides conventional indicators like WBC, percentage of polymorphonuclear neutrophil(PMN%), IL-6, and CRP, the combination of serum and joint fluid markers can significantly enhance the diagnostic accuracy [129–131]. In recent years, the application of emerging biomarkers and the improvement of diagnostic standards have further improved diagnostic accuracy. However, in terms of sensitivity and specificity, synovial PMN% and WBC still remain irreplaceable position [102, 105].

Leukocyte esterase(LE) serves as a direct indicator of neutrophil activation. The LE test offers advantages such as rapidity, low cost, high sensitivity(90–95%), and high specificity(85–90%). Since 2013, it has been included as an important reference indicator in the subsidiary criteria established by international consensus for diagnosing PJI [132, 133]. However, it should be noted that this is a qualitative test, and interpretation is difficult when the result is an intermediate result. Enzyme activity may be diluted by bloody taps, leading to false-negative results [105]. Thus, LE has some practical limitations.

Alpha-defensin(AD), which is naturally secreted by activated neutrophils and possesses both broad-spectrum antimicrobial and diagnostic functions, was incorporated as a reference indicator in the diagnostic criteria in 2018. A meta-analysis demonstrated that AD had comparable diagnostic efficacy to LE(sensitivity 88–92%, specificity 90–94%) [134]. Kuo et al. evaluated the diagnostic performance of the secondary criteria of the 2018 ICM for chronic PJI in Asian populations and found that joint fluid α-defensin showed the best diagnostic performance [123]. However, it should be noted that false-positive

results may occur in the presence of metal deposition disorders, and false-negative results may arise when there are low-virulence microorganisms [135].

Calprotectin is a specific marker of neutrophil activation. It has exhibited excellent performance in the diagnosis of PJI, with a specificity of 84–99%, and a sensitivity of 84–98%. It is inexpensive and easy to obtain, endowing it with great application potential [136, 137]. Several studies have indicated that the diagnostic value of calprotectin is superior to that of AD, LE, CRP, and other indicators, making it a promising biomarker for the auxiliary diagnosis of PJI [138–141]. Nevertheless, it has not been included in the recognized guidelines yet, and more evidence-based studies are required to facilitate its clinical application.

In recent years, D-lactate has been a biomarker attracting significant attention in PJI diagnostic studies. Several studies [142–144] have shown that its diagnostic efficacy is comparable to or even higher than that of WBC, LE, FIB, and ESR, with a sensitivity of 82-90.7%, and a specificity of 76–100%. If more data can support it, it is expected to become one of the auxiliary diagnostic indices for PJI in the future. Additionally, exploratory studies on markers such as presepsin [145], lipid transporter proteins(LCN2, NGAL) [146, 147], cell-free DNA(cfDNA) [148], and interleukin-1β(IL-1β) [149] are underway, although their clinical value has not been fully validated yet.

Microbial culture Microbial culture remains one of the gold standards for the diagnosis of PJI. For patients with chronic infections or a history of antibiotic exposure, sonication combined with blood culture bottles has been established as the preferred approach [105]. However, due to biofilm formation, a subset of cultures still fail to yield the causative pathogens [150, 151]. To enhance infection detection, novel diagnostic approaches are being investigated.

Molecular biology techniques, including polymerase chain reaction(PCR), metagenomic next-generation sequencing(mNGS), and fluorescence in situ hybridization(FISH), enable rapid and accurate detection of pathogen DNA. However, false-positive results are likely to occur(e.g., due to sample contamination or interference from dead bacterial DNA), and clinicians face challenges in determining the authenticity of positive molecular test results when traditional culture yields negative outcomes. Additionally, most current technologies cannot directly provide antimicrobial susceptibility profiles and require combination with microbial culture for clinical therapeutic guidance. Owing to high costs, vulnerability to sample contamination, lack of standardized probes/primers, and absence of clear interpretative criteria, these techniques are predominantly indicated for culture-negative cases and have not been integrated into routine diagnostic protocols [105, 152–156].

Ultrasound technology was incorporated into diagnostic guidelines in 2021 owing to its cost-effectiveness and biofilm-destructive capacity, which have rendered it a prominent research focus. It is recognized as an essential adjunctive modality for patients with chronic infections, culture-negative infections, or recent antibiotic exposure, particularly in challenging diagnostic scenarios. However, it is not currently recommended as a routine diagnostic modality [105]. Trampuz et al. [157] discovered that treating removed prostheses with ultrasound could release bacteria encapsulated within the biofilm. This approach increased the culture sensitivity from 60.8 to 78.5% and the specificity to 98.8%. It enabled the effective isolation of pathogens even when antibiotics had been administered preoperatively. It has also been demonstrated [158, 159] that combining ultrasound with PCR can further boost the sensitivity to 95% and the specificity to 97%, which is significantly more effective than using tissue culture or molecular testing alone in terms of sensitivity and specificity. However, for diagnostic purposes, low-intensity ultrasound is recommended. High-intensity ultrasound may lead to bacterial death [160]. Generally, frequencies ranging from 20 to 200 kHz are regarded as low intensity, while frequencies exceeding 1 MHz are considered high intensity [161].

Histopathologic examination

Histopathological examination is considered one of the gold standards for diagnosing PJI. In 5 consecutive high-power fields(×400), infection is directly diagnosed if each field exhibits ≥ 5 neutrophils; ≥ 5 neutrophils in a single field indicate likely infection, requiring comprehensive judgment based on other evidence [105]. With extremely high specificity, this examination alone can confirm infection when confirmatory tests are positive [105]. However, sensitivity is influenced by multiple factors: pathologist's experience, surgical specimens' quality, and PJI clinical features(e.g., culture-negative infection, chronic infection, low-virulence bacterial colonization) [105]. Stroh et al. demonstrated 97% consistency between intraoperative frozen and permanent sections for hip PJI diagnosis, with frozen section sensitivity at 59%. Sensitivities reported in other studies ranged from 29 to 100% [162].

Studies show that while preoperative biopsy alone had 62% sensitivity and 97% specificity, combining it with microbial culture significantly improved diagnostic accuracy to 90% sensitivity and 97% specificity [163]. Blood culture bottles remain among the most validated culture methodologies, particularly for patients with chronic infections or a history of antibiotic therapy [105]. Nonetheless, preoperative biopsy is recommended as a routine

procedure, as its results facilitate advance planning of antibiotic therapy and improve surgical outcomes [164].

Intraoperative frozen section biopsy is characterized by rapid results and high diagnostic utility, providing surgeons with intraoperative pathological evidence to inform surgical decision-making. However, a negative result cannot entirely exclude infection and should be interpreted in conjunction with other evidence [165]. During surgery, apart from synovial fluid, at least five reliable tissue samples should be obtained with separate instruments, with priority assigned to samples containing bone-implant interface membranes. The detection rate can be further improved by sonication of samples [105].

Postoperative pathological examination also serves as a crucial basis for PJI diagnosis. When combined with microbiological culture, it further enhances diagnostic accuracy, providing critical support for confirming infection and guiding treatment planning [164].

Imaging

Imaging serves as an adjunct in diagnosing postoperative infections. Early X-rays generally lack characteristic manifestations, yet they can be utilized to exclude non-infectious complications like prosthesis loosening and displacement [166]. Magnetic resonance imaging(MRI) demonstrates high sensitivity to bone marrow edema and soft tissues, rendering it an ideal tool for evaluating peripheral soft tissue lesions [167]. However, MRI image quality is significantly compromised by metal artifacts induced by implanted devices, severely restricting its utility in this area [168]. In recent years, the development of metal artifact reduction sequence MRI(MARS-MRI) has pioneered novel approaches to diagnostic applications in PJI [169, 170]. Notwithstanding, widespread clinical implementation of this technology is hindered by lack of sufficient clinical validation and the absence of standardized diagnostic protocols.

The 2021 EBJIS consensus emphasized the critical role of nuclear imaging techniques in diagnosing PJI, while highlighting their inherent limitations: sterile prosthesis loosening or the early postoperative period may induce false-positive isotope uptake, indicating that non-infectious factors can lead to abnormal radionuclide accumulation. Thus, the diagnostic reliability of three-phase bone scintigraphy is closely associated with postoperative duration, with results considered reliable only beyond 2 years following hip arthroplasty and 5 years following knee arthroplasty [171]. At this stage, a negative result provides strongly exclusion of infection, whereas positive results require additional tests for further diagnosis, positioning this technique as an exclusionary diagnostic tool for chronic PJI [105]. Recent advancements in nuclear imaging technology(notably leukocyte scintigraphy) have substantially improved diagnostic accuracy. Positive criteria for leukocyte scintigraphy include progressive accumulation of labeled white blood cells at 3–4 h and 20 h post-injection, which strongly suggests infection. When combined with bone marrow scintigraphy, non-specific uptake is minimized, further reducing the false-positive rate [172, 173]. Although FDG-PET has been reported for PJI diagnosis [174], a standardized diagnostic protocol remains undefined due to the absence of unified interpretation criteria.

Moreover, color ultrasound of the inguinal lymph nodes holds promise for diagnosing PJI. Qin et al. [175] prospectively recruited 176 patients undergoing primary or revision hip or knee arthroplasty. All patients underwent preoperative inguinal lymph node ultrasound, and the results indicated that inguinal lymph node ultrasound is a promising method for diagnosing PJI and assessing persistent infections. However, more high-quality studies are needed for further confirmation.

Management of treatment strategies for PJI

Antibiotic therapy

Antibiotic therapy remains central to the management of PJI. Once PJI is diagnosed, a treatment plan should be individualized based on pathogen type, infection extent, and patient characteristics. Antibiotics selected for therapy should demonstrate biofilm penetrance, optimal skeletal distribution, and high bioavailability. Representative agents include rifampin, fluoroquinolones, and daptomycin [176, 177].

Antibiotic administration routes

Antibiotics are typically administered intravenously; however, systemic administration may fail to achieve tissue concentrations exceeding the minimum inhibitory concentration(MIC), thereby reducing therapeutic efficacy [178]. In chronic or refractory infections, local delivery strategies can enhance site-specific drug concentrations while minimizing systemic exposure and adverse effects. Common approaches include proximal tibial intraosseous(IO) antibiotic therapy [179, 180], intra-articular infusion technique [181, 182], intra-wound vancomycin powder application(IVP) [183, 184], and antibiotic-loaded bone cement(ALBC) [65]. However, the clinical utility of these techniques in PJI requires further validation. Recent evidence indicates that intra-wound vancomycin powder or ALBC may not confer benefits for PJI management [185, 186].

Empirical antibiotic therapy

Treatment protocols for PJI vary according to disease stage. In early postoperative PJI, characterized primarily by mixed infections, surgical debridement is expedited, and a broad-spectrum β-lactam regimen combined with

agents active against Gram-positive cocci is administered [187].

Acute hematogenous PJI, almost exclusively monomicrobial, is commonly caused by methicillin-sensitive *Staphylococcus aureus*(MSSA) and *Streptococcus* species. First-line antibiotics include cefazolin or cloxacillin; third-generation cephalosporins are recommended for suspected Gram-negative bacillary infections. Identification and eradication of the infection source are central to treatment [188].

Chronic PJI rarely requires emergency surgery, so the priority of treatment strategies is to confirm the diagnosis and isolate the pathogen. In patients with prior treatment history in other hospitals, initial antibiotic regimens may reference previous culture results. Late-stage chronic PJI, often caused by low-virulence coagulase-negative *Staphylococcus*(CNS), does not warrant routine broad-spectrum combination therapy [188].

For severe cases, early initiation of empirical broad-spectrum antibiotic therapy combined with aminoglycosides is advised to expand antimicrobial coverage [189].

Targeted antibiotic therapy

Once pathogen culture and antibiotic susceptibility testing results are confirmed, therapy should transition from empirical to pathogen-targeted regimens. It has been demonstrated in studies [190–192] that pathogen type is significantly associated with treatment outcomes in PJI. Treatment difficulty-based classification(difficult-to-treat, DTT vs. non-DTT) directly informs clinical decision-making, facilitates prognosis assessment, and guides optimization of antibiotic selection, administration routes, and treatment duration.

DTT pathogens refer to those lacking effective antibiotics with anti-biofilm activity, are only sensitive to drugs with low oral bioavailability, or are difficult to diagnose and treat due to characteristics such as slow growth or intracellular parasitism. Infections caused by such pathogens often recur due to insufficient clearance efficiency of oral medications, resulting in poor prognosis. Early identification and stricter antimicrobial regimens, along with proactive intervention measures, are necessary [192, 193]. Treatment protocols should be developed through multidisciplinary collaboration among microbiologists, pathologists, and orthopedic surgeons, and adjusted dynamically based on antimicrobial susceptibility test results [190, 192]. According to the definition by Wimmer et al. [190], DTT encompasses the following pathogens.

①*Staphylococcus* species resistant to rifampin, fluoroquinolones, and other highly active antibiotics are classified as DTT. According to guidelines, treatment protocols recommend intravenous administration of vancomycin, but it presents several challenges related to its administration, including the need for slow infusion, significant side effects, and the requirement for periodic serum level monitoring to ensure therapeutic concentrations [194, 195]. Alternative therapeutic agents include daptomycin and linezolid [196]. Additionally, teicoplanin allows for simpler bolus administration and has fewer side effects compared to other glycopeptides. These features make teicoplanin a suitable and effective choice in the treatment of PJI [197].

②*Staphylococcus* species resistant to trimethoprim/sulfamethoxazole, doxycycline, and linezolid are classified as DTT, primarily due to the limited oral bioavailability of alternative agents. Treatment for such isolates necessitates intravenous administration of agents like vancomycin [196]. Similarly, ampicillin-resistant *Enterococcus* species are categorized as DTT owing to the limited oral bioavailability of alternative agents, with intravenous vancomycin typically required for treatment [194].

③Fluoroquinolone-resistant *Pseudomonas* species, susceptible only to intravenous antibiotics(e.g., cefepime), are classified as DTT [194]. Azole-resistant yeasts require intravenous echinocandin therapy(e.g., caspofungin), and are classified as DTT [198]. Extended-spectrum β-lactamase(ESBL) - or AmpC-producing *Enterobacterales*, resistant to β-lactams and often co-resistant to fluoroquinolones, are sensitive exclusively to intravenous agents. Preferred treatment includes intravenous carbapenems, classifying them as DTT [199, 200]. *Acinetobacter spp.* (e.g., *Acinetobacter baumannii*), highly resistant to fluoroquinolones(e.g., levofloxacin), are classified as DTT. Optimal therapy consists of intravenous sulbactam/durlobactam combined with carbapenems [201].

④Small colony variants(SCVs), characterized by slow growth, robust biofilm formation, and high intracellular persistence, exhibit enhanced ability to evade antimicrobial therapy. Combination therapy and prosthetic removal are required for management. Rifampin combined with fluoroquinolones is recommended as first-line treatment [202], classifying SCVs as DTT. Nutritionally variant streptococci(NVS; *Abiotrophia spp*. and *Granulicatella spp.*), slow-growing microorganisms requiring specialized culture conditions, necessitate prolonged treatment courses. Vancomycin monotherapy or combination with aminoglycosides is recommended [203], classifying NVS as DTT.

⑤*Propionibacterium acnes*(*P. acnes*), challenging to detect and eradicate, is classified as DTT. Management necessitates thorough surgical debridement and prolonged antibiotic therapy. Penicillin or ceftriaxone are recommended as first-line agents [194].

Non-DTT pathogens are defined as those susceptible to antibiotics with anti-biofilm activity and oral agents with high bioavailability, such as rifampin and

fluoroquinolones. Infections caused by these pathogens in prosthetic joints are associated with higher infection clearance rates and improved clinical outcomes [192]. Common non-DTT pathogens include MSSA, *Streptococcus* species, and penicillin-susceptible *Enterococcus* species.

For MSSA, initial intravenous therapy should consist of anti-staphylococcal β-lactam antibiotics(e.g., nafcillin or cefazolin). Efficacy can be optimized through high-dose continuous intravenous infusion [194]. Following 3–5 days of clinical improvement, rifampin(intravenous or oral) is added to the regimen for a combined therapy duration of 1 week. If clinical improvement persists, gastrointestinal tolerance is confirmed, and the patient comprehends the treatment plan, therapy may be transitioned to oral levofloxacin in combination with rifampin [204, 205].

For *streptococcal* infections in non-allergic patients, amoxicillin is the preferred agent [206]. High-dose intravenous administration with extended infusion duration is recommended, and the agent is suitable for the oral phase of sequential therapy. Combination therapy for *streptococcal* PJIs is not recommended by international guidelines, as it fails to improve outcomes while increasing the risk of adverse events [194, 207].

For infections caused by penicillin-sensitive *Enterococcus* species, high-dose intravenous penicillin or ampicillin, often combined with gentamicin for synergistic activity, is recommended by international guidelines [194]. It has been demonstrated in studies [187] that for non-allergic patients with amoxicillin-sensitive isolates, the preferred treatment regimen consists of intravenous amoxicillin for 2–4 weeks, followed by sequential oral therapy.

Antibiotic therapy duration

Given that this content will be revisited in the subsequent surgical intervention section, it has been tabulated in Table 4 for reference [194].

Surgical intervention

Surgical intervention for PJI is typically required and encompasses debridement, antibiotics, and implant retention(DAIR), one-stage/two-stage revision arthroplasty, or salvage surgery.

Debridement, antibiotics, and implant retention(DAIR)

Compared with revision arthroplasty, DAIR is associated with advantages of implant preservation, lower complication rates, and cost-effectiveness. It is indicated for acute PJI without implant loosening, multidrug-resistant infections, or immunocompromise, including early postoperative infections(≤ 1 month) and late acute hematogenous infections(≥ 3 months postoperatively but with symptoms < 3 weeks and no sinus tract) [194]. DAIR typically comprises thorough debridement of periarticular soft tissues, exchange of the polyethylene liner, intraoperative local antibiotic implantation, and retention of a stable prosthesis [194, 208]. Early intervention is critical to acute PJI management. It has been demonstrated in biofilm models that bacterial antibiotic sensitivity declines over time, with biofilm maturation occurring within 7 days [209]. Thus, prompt initiation of DAIR after diagnosis is recommended [210]. Surgical indications for DAIR must be strictly controlled [194]. The KLIC or CRIME80 scoring systems are used to assess DAIR success rates for clinical decision-making [211].

Postoperative empirical antibiotic therapy is initiated. Upon confirmation of pathogen identification and antimicrobial susceptibility, therapy is adjusted to pathogen-targeted intravenous or oral agents with high bioavailability for a 4-6-week course. For *Staphylococcus*

Table 4 Antibiotic therapy duration

Types of Surgery	S.	IV or PO	Sequential Therapy	Total Duration
DAIR	NO	4-6 wk	\	\
	YES	2-6 wk (If rifampin susceptible: combine oral; if contraindicated: IV antibiotics 4-6 wk, no extended course.)	Rifampin+companion drug to full course	THA:3 mo; TKA:6 mo
1-stage exchange	NO	4-6 wk	\	\
	YES	2–6 wk (If rifampin susceptible: combine oral; if contraindicated: IV antibiotics 4-6 wk, no extended course.)	Rifampin+companion drug to full course	THA:3 mo
2-stage exchange	\	4–6 wk	\	\
Knee arthrodesis	\	4–6 wk	\	\
Resection arthroplasty	\	4-6 wk, 6 wk for more virulent organisms (e.g., *S. aureus)*	\	\
Amputation	\	24-48 h (for thorough debridement of infection)；4-6 wk (for residual infection)	\	\

infections, intravenous antibiotics plus oral rifampin(if sensitive) are administered simultaneously for 2–6 weeks, followed by sequential combination therapy with rifampin and a companion oral agent for a total duration of 3 months [194]. In cases where rifampin is contraindicated, intravenous antibiotics are administered for 4–6 weeks without duration extension. For DTT pathogens sensitive only to intravenous antibiotics, full 6-week intravenous administration is recommended, with adjustments guided by antibiotic susceptibility testing results [190, 192].

It has been demonstrated that DAIR success rates in acute postoperative PJI are significantly higher than those in acute hematogenous PJI [212, 213]. This discrepancy is attributed to the clear onset timing and prompt intervention in acute postoperative cases, whereas acute hematogenous PJI typically occurs > 3 months after arthroplasty, often presenting with indistinct symptom onset and comorbid bacteremia [214]. For preoperatively confirmed DTT, two-stage revision arthroplasty is recommended as the first-line approach [192, 194].

For two-stage DAIR, Chung et al. [215] demonstrated that a two-stage DAIR protocol achieved a higher infection control rate than traditional one-stage debridement with modular component exchange. McQuivey et al. [210] also reported significant clinical advantages of two-stage over one-stage DAIR. Conversely, studies by Perez et al. [216] and Moojen et al. [217] showed no significant improvement in implant retention rates with two-stage DAIR compared to one-stage procedures. The clinical value of two-stage DAIR remains controversial, as outcomes are influenced by clinical context, pathogen complexity, and patient-specific factors. Further high-quality research is required to validate these findings.

For repeat DAIR, Wouthuyzen-Bakker et al. [218] analyzed 455 cases of acute PJI and reported a 25.7% failure rate for repeat DAIR, with most patients successfully retaining the implant. Conversely, Lin et al. [219] demonstrated that repeat DAIR had a significantly lower success rate than initial DAIR, increasing the risk of failure and reinfection in two-stage exchange arthroplasty. This finding was corroborated by two additional studies [220, 221]. In summary, current evidence suggests that clinical decision-making regarding repeat DAIR should exercise caution.

Prosthetic replacement

In cases of chronic or advanced infections, especially when complicated by prosthetic loosening or biofilm formation, simple debridement alone is frequently insufficient to achieve therapeutic efficacy. Therefore, prosthetic replacement surgery, including one-stage or two-stage revision arthroplasty, is indicated.

One-stage exchange is indicated primarily in patients with PJI after THA, where pathogens are susceptible to oral antibiotics, local tissue conditions are favorable, and without severe bone defects [194, 222]. The procedure involves removal of the infected prosthesis, thorough debridement of the surgical site, and implantation of a new prosthesis, supplemented by local antibiotic application. Postoperative intravenous or oral antibiotics with high bioavailability therapy are administered for 4–6 weeks. For *Staphylococcus* infections, concomitant administration of intravenous antibiotics and oral rifampin is recommended for 2–6 weeks(if susceptible). Following intravenous therapy discontinuation, sequential therapy with rifampin combined with a companion oral agent is advised to ensure a total treatment duration of 3 months [194]. In cases of rifampin contraindication, exclusive intravenous therapy for 4–6 weeks without duration extension is indicated. This surgical procedure has been increasingly recognized for its advantages of shortened treatment duration and rapid recovery [5, 223]. As demonstrated in Zhao et al.'s [224] meta-analysis, no significant differences were observed in reinfection or reoperation rates between one-stage and two-stage revision arthroplasty. However, due to limitations in inclusion/exclusion criteria and study heterogeneity, these conclusions warrant further validation via prospective randomized trials. Another investigation [225] reported comparable reinfection rates between the two approaches(7.6% vs. 8.8%), findings highlighting the urgent need for high-quality research to refine indications for one-stage revision.

Two-stage exchange is the gold standard for treating PJI, indicated for patients with severe infection, prosthetic instability, staged infection control requirements, or DTT pathogens [194, 226]. The first stage entails complete removal of the infected prosthesis and debridement, with subsequent implantation of an antibiotic-loaded cement spacer [227]. Postoperative targeted intravenous or high-bioavailability oral antibiotics should be administered for 4–6 weeks [194]. Antibiotics should be discontinued 2–8 weeks before surgery to ensure intraoperative culture accuracy [190, 194].

The reimplantation interval for PJI is determined by infection control status. A review by Puetzler et al. [228] has shown that shorter reimplantation intervals may correlate with improved clinical outcomes, as reduced drug-eluting capacity of the spacer may facilitate bacterial recolonization, and shorter intervals can minimize patient immobilization time. Currently, the mean two-stage interval ranges from 80 to 100 days, though the optimal interval remains undefined [229–231].

The timing of reimplantation in two-stage arthroplasty should be determined by comprehensive assessment of clinical symptoms, inflammatory markers(CRP,

ESR), imaging findings(e.g., periosteal reaction, abscess), joint aspiration, and culture results [194]. If infection is suspected based on clinical symptoms or inflammatory markers preoperatively, joint aspiration may be performed [194]. Reimplantation may proceed when preoperative ancillary tests show no abnormalities and wound healing is unremarkable. Intraoperatively, frozen section pathology(≥ 3 tissue samples) and bacterial culture should be conducted to confirm absence of infection [190, 194, 232]. The scoring system proposed by Tiziana et al. [233] —including negative local symptoms, normal CRP/ESR, synovial WBC count < 952/mL, neutrophil percentage < 52%, and D-dimer < 1100 μg/mL—may inform reimplantation decisions, though its clinical utility requires further validation.

Following confirmation of infection control, prophylactic antibiotics are required only during the second-stage reimplantation of the new prosthesis. If infection is suspected during second-stage surgery, debridement with continuation of the initial antibiotic regimen is indicated for mild cases, whereas prosthesis removal and restart of the two-stage process are recommended for severe cases [194]. High-risk patients(e.g., immunosuppressed individuals or those with drug-resistant bacterial infections) may require individualized treatment protocols [194]. Although two-stage revision arthroplasty achieves high infection control rates, patients remain in a non-functional joint state for an extended period, which increases surgical-related morbidity and delays functional recovery [107, 226, 234, 235].

Differentiated antibiotic strategies are established by IDSA guidelines based on *Staphylococcus* and non-*Staphylococcus* PJI, with personalized treatment plans recommended for difficult-to-eradicate pathogens(e.g., *P. acnes*), highly virulent pathogens(e.g., *Staphylococcus aureus*), drug-resistant bacteria(e.g., MRSA), and patients' systemic conditions(e.g., immunocompromised individuals). Similarly, the DTT pathogens classification system for management of PJI also demonstrates significant potential [190–193], while current evidence remains limited. Given the high antibiotic resistance, treatment complexity, and recurrence rates associated with DTT pathogen infections, heightened vigilance is warranted for orthopedic surgeons, who should adopt proactive, individualized treatment strategies. Future high-quality studies are needed to further explore the classification's utility in antibiotic selection, treatment duration, and combination therapy for PJI, thereby furnishing stronger evidence to optimize treatment protocols.

Salvage surgery

For PJI cases with multiple failed revisions and severe infection-related morbidities on patients, salvage surgeries including knee arthrodesis(KA), above-knee amputation(AKA), knee resection arthroplasty, Girdlestone arthroplasty, hip disarticulation, and persistent fistula may be considered.

Yeung et al. [236] reported that KA has been demonstrated as a durable and effective salvage option for infected TKA, with an infection control rate of 94.1% at a minimum of 2 years postoperatively. Most patients were able to remain ambulatory postoperatively, and the probability of progression to AKA was low. Similarly, Conway et al. [237] found that better functional outcomes after KA were observed in shorter patients with lower BMI and younger age, establishing it as a viable alternative to amputation for patients with infected TKA and providing satisfactory functional results. Hoveidaei et al. [238] noted that both KA and AKA have been identified as viable salvage options for PJI, each with distinct advantages and disadvantages. Surgeons should thoroughly discuss these options with patients, consider their individual circumstances, and select the most appropriate surgical approach after comprehensive evaluation.

Knee resection arthroplasty is a salvage procedure for persistent infections following TKA. This procedure involves the removal of infected prostheses and foreign bodies, thorough debridement of the surgical site to control infection, and has been demonstrated as an effective approach for eradicating infection, preserving the limb, and maintaining basic activities of daily living [239]. A recent study [240] showed that when used to treat persistent infections, knee resection arthroplasty achieved infection eradication in 84% of patients, with 45% able to ambulate in community settings(all requiring brace and walker support). This provides a limb-sparing option for patients who cannot tolerate knee fusion or amputation.

Girdlestone arthroplasty was developed by Girdlestone in 1928 and initially applied for the treatment of hip tuberculosis during the pre-antibiotic era. It was later gradually adopted for patients with PJI [241]. Boure [242] performed Girdlestone arthroplasty on 33 patients with PJI and conducted a 6.2-year follow-up. The results demonstrated an infection control rate of 97% and a pain relief rate of 91%, indicating that this procedure has been proven highly effective in controlling infection and alleviating pain. It remains a reasonable salvage option for complications following hip surgery.

Hip disarticulation is a radical amputation procedure indicated for life-threatening conditions or the management of severe infections, bone defects, or vascular damage involving soft tissues and bone [243]. Fenelon et al. [244] analyzed 11 patients with PJI, the majority of whom had undergone multiple prior surgeries and ultimately required hip disarticulation due to severe infection, bone defects, or vascular injury. Postoperative functional recovery was achieved in some patients, demonstrating that this procedure can effectively preserve life and

improve quality of life when PJI pose a life-threatening risk or lead to complete limb function loss.

Persistent fistula(PF) may also be considered a salvage measure, whereby continuous drainage of the infected site is maintained through preservation of a fistula(natural or artificially created) to prevent infection spread. The procedure can be carried out within 30 min under spinal anesthesia, and is a minimally invasive one-stage salvage option for frail patients [245]. A retrospective analysis by Troendlin et al. of 159 patients with PJI treated with PF revealed poor efficacy and frequent complications, highlighting that PF should be reserved for frail patients with limited life expectancy and requires careful consideration [246]. In contrast, a multicenter study by Klim et al. demonstrated that PF represents an acceptable salvage option for select patients with refractory osteoarticular infections; although physical function limitations exist, patient psychological status and quality of life remain tolerable [247].

Suppressive antibiotic therapy(SAT)

Chronic suppressive therapy represents a non-curative strategy for PJI patients unable to undergo or refusing surgery. It is employed with prolonged(even lifelong) oral antibiotics for infection control, aimed at suppressing progression, relieving symptoms, preventing acute episodes, and maintaining low infection activity [194].

In SAT, antibiotic selection should be based on a comprehensive assessment of oral bioavailability, patient tolerance, and antimicrobial activity against pathogens. Commonly used regimens include β-lactam monotherapy, sulfonamides, tetracyclines, and rifampin-based combination therapy [194, 248, 249]. Currently, no clear definition exists for the optimal timing of SAT discontinuation. It has been demonstrated in recent studies that failure rates do not differ significantly between 1-year and longer SAT durations, with reassessment recommended after 1 year to guide treatment continuation [250, 251]. Given the risk of adverse events associated with long-term therapy, dynamic monitoring of efficacy and drug toxicity is essential [252]. Notably, a meta-analysis showed that only 4.3% of patients discontinued SAT due to adverse events, indicating overall favorable safety of the therapy [253].

The success rate of SAT exhibits significant variation(23%-86%), primarily influenced by factors including infection type(higher success rates are associated with acute infections), pathogen type(Gram-positive cocci are more readily controlled), and patient comorbidities [254]. Recent research has investigated SAT application in *streptococcal* PJI, reporting a 7.5-year infection-free survival rate of 62%, which is superior to the 38% observed in the non-SAT group. These findings suggest that suppressive therapy can improve long-term outcomes in streptococcal PJI, with SAT emerging as a viable long-term treatment strategy for selected patients [255].

Future research directions

Currently, surgical procedures combined with antibiotics remain the standard treatment for PJI(Table 5), yet its efficacy is constrained. The formation of bacterial biofilms on prosthetic surfaces represents a primary challenge in therapy. Extracellular polymeric substances(EPS) secreted by these biofilms establish a physical protective

Table 5 Management of treatment strategies for PJI

Treatment strategies	Specific methods	Applicable situation
Antibiotic therapy	Empirical therapy	After diagnosing PJI when the pathogen is not yet identified[187-189].
	Targeted therapy	After the pathogen culture results are determined[190-207].
	Antibiotic therapy duration	To reduce the risk of infection recurrence[194].
Surgical treatment	DAIR	Early postoperative infections (≤1 month) and late acute hematogenous infections (≥3 months postoperatively but with symptoms＜3 weeks and no sinus tract)[190.192.194.208-221].
	One-stage revision	For patients with well-controlled infection and favorable local soft-tissue conditions[5.194.222-225].
	Two-stage revision	For chronic or late-stage infections, especially in cases with loosened implants or periprosthetic membrane infections[107.190.194.226-235].
	Salvage surgery	For patients with repeated revision failures and whose daily life is severely affected by the infection[236-247].
Antibiotic therapy	SAT	For patients unable to undergo or refusing surgery[194.248-255].

Table 6 The future research directions of PJI

Research directions	Specific techniques or methods	Research status and challenges
New antibiotics[259-272]	Research of new generation drugs; Exploration of the use of newly approved antibiotics in PJI.	Microbial resistance has driven the urgent need for antibiotic research and development. Some new agents like Olivancin and Dabavancin show promise, but their effectiveness in PJI requires verification through large-scale studies.
Drugs targeting dormant acteria[273-278]	Stimulation of dormant state bacterial metabolism or direct targeting of dormant cells.	Existing therapeutic strategies have limitations; stimulation of dormant bacterial metabolism may exacerbate infections, and ADEP4 application is limited by lack of cellular proteins and the spread of drug-resistant strains.
Immunotherapy[279-292]	Monopolyclonal antibodies target different stages of bacteria for immunization; polyclonal antibodies targeting SesC against biofilms.	Immunotherapy has shown some promise in the study of biofilm infection treatment. Immunotherapy is mainly in the research stage, large-scale preparation is difficult and costly, and its effectiveness and safety need to be further verified.
Phage therapy[293-302]	Utilization of phages and their production of endolysins and EPS depolymerases.	Phage therapy has potential in PJI treatment research, but its high specificity means multiple strains are needed for mixed infections, and its independent efficacy in PJI remains unconfirmed.
Biofilm-targeted intervention therapies[303-314]	Enzyme therapies (dispase B, Protease K, DNase 1), D-amino acid.	Enzyme therapies have inhibitory effects on biofilms. However, they are still far from widespread clinical application.
Ultrasound[105.315-324]	Low-intensity ultrasound aids in diagnosis;high-intensity ultrasound is applied to eliminate bacterial biofilms; the combination of ultrasound and antibiotics has a synergistic anti-biofilm effect.	Ultrasound therapy is at an emerging stage and has potential for diagnosis and treatment, but the optimal treatment duration, frequency and other parameters need to be explored and optimized in a large number of studies.
Electrochemical methods[325-329]	Cathodic Voltage-Controlled Electrical Stimulation，electrochemical scaffolds, electric current applications, and electrothermal therapy.	Electrochemical methods have been used in antimicrobial research. However, the effectiveness and safety of clinical application is to be explored.
Implant surface modification	Nanoparticle-coated implants[61.62.330-347](silver ions, iodine, copper ions, selenium and zinc oxide).	Nanoparticles are effective in antimicrobial and promoting osseointegration, but long-term safety, precise control of synthesis, release and loading require solution.
	The defensive antimicrobial coating[348-353].	DAC offer promising strategies for the prevention and treatment of PJI. However, it is necessary to optimize coating retention technology, explore the optimal antibiotics and their combinations, and ensure validation by additional high-quality clinical investigations.
	NO[354-356], Chitosan[357-359], AMPs[360.361]	NO, chitosan, and AMPs all have great potential in the prevention and treatment of PJI. However, they face issues such as instability, lack of large-scale clinical trials, and high costs.
Drug delivery system[362-377]	Antibiotic delivery carriers loaded with antibacterial agents are added to the articular cavity or bone cement.	Microparticles or nanocapsules are potential in the field of antibiotic delivery, but the biocompatibility of carrier materials, drug release control and long-term safety need to be studied in depth. The clinical value of CS or CHA + CS in PJI requires to be further confirmed.
Vaccines[378-381]	Vaccines with IsdB and the E2 subunit of the PDHC as antigens.	Positive results have been achieved in animal experiments, but human clinical trials have not been successful yet. It is necessary to study the human immune mechanism and establish appropriate experimental models.
Machine learning models[382-385]	Construct a model using multi-faceted data of patients.	It has broad application prospects, but it is still in the research stage. The accuracy, practicality, and other aspects of the model require more research for verification.

barrier and induce bacteria into a spore-like dormant state. In this metabolically quiescent state, antibiotics targeting cell wall synthesis(e.g., β-lactams) or nucleic acid metabolism(e.g., fluoroquinolones) are rendered nearly inactive, with minimum inhibitory concentrations(MICs) elevated by several thousand-fold [256–258]. Consequently, there is an urgent need to explore novel treatment strategies(Table 6), which has emerged as a key issue in arthroplasty research.

New antibiotics

As antimicrobial resistance escalates, the demand for novel sensitive antibiotics has become increasingly pressing. To address this challenge, alongside the development of new antibiotics, the accelerated application of newly approved agents' treatment in PJI is of critical importance.

New cephalosporin-class agents, including novel iron-carrier cephalosporins(e.g., cefiderocol) and fifth-generation cephalosporins(e.g., ceftaroline fosamil, ceftobiprole), have shown significant advantages in antimicrobial therapy. Cefiderocol, a catechol-iron carrier cephalosporin, was approved by the US Food and Drug Administration(FDA) in 2019 and the European Medicines Agency in 2020 for treating adult complicated urinary tract infections and Gram-negative bacterial infections [259]. It offers a new strategy against carbapenem-resistant microbes(e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, carbapenem-resistant *Enterobacteriaceae*) [260]. Ceftaroline fosamil, the first fifth-generation cephalosporin approved by the US FDA in 2010, is indicated for community-acquired pneumonia and complicated skin/soft tissue infections in adults and children [261]. Ceftobiprole, approved in 2014, is primarily used for complicated skin/soft tissue infections and community/hospital-acquired pneumonia [262]. Both agents cover Gram-positive bacteria(e.g., MRSA) and selected Gram-negative pathogens, exhibit good tolerability, and have seen expanding clinical applications [263]. Although the application of new cephalosporins in PJI remains in the exploratory stage [264, 265], their antibacterial activity has been demonstrated. Given their unique antimicrobial spectra and mechanisms, they are expected to become important strategies for drug-resistant PJI treatment.

In recent years, the US FDA has also approved three new antibiotics targeting Gram-positive bacteria, including MRSA: dalbavancin [266], oritavancin [267], and telavancin [268]. Although these three drugs are primarily indicated for skin infections, they all exhibit the ability to penetrate bone and joint tissues. Currently, dalbavancin has been utilized clinically for treating *staphylococcal* PJIs [269] and a case of PJI caused by *Corynebacterium striatum* infection [270]. Studies have reported an overall clinical cure rate of 73% for *staphylococcal* PJIs treated with dalbavancin; however, its efficacy requires further validation through larger-scale clinical trials [269]. As for olivancin [271, 272] and tilavancin [268], while they have demonstrated certain antimicrobial activity in in vitro studies or animal models, which holds potential value for PJI treatment, additional research is needed to confirm their effectiveness in clinical practice. Future in-depth exploration of the efficacy of these antibiotics against PJI is anticipated to open up new directions for antibiotic-based treatment strategies for this condition.

Drugs for dormant bacteria

In the management of PJI, dormant bacteria, also known as persister cells, present a significant therapeutic challenge. These bacteria are metabolically inactive, making them highly tolerant to antibiotics.

Currently, two primary therapeutic strategies exist for tackling such bacteria. The first strategy involves stimulating the metabolism of dormant bacteria to enhance their susceptibility to antibiotics. For instance, supplying a nutrient-rich fresh medium to the biofilm of MSSA can increase the bacteria's susceptibility to oxacillin [273]. However, this approach carries the risk of exacerbating the infection. The second strategy focuses on directly targeting dormant cells. The antibiotic ADEP4 serves as an example, it activates the cytoplasmic ClpP protease in dormant *Staphylococcus aureus* bacteria, leading to the non-specific degradation of over 400 intracellular protein targets, including ribosomal proteins and various metabolic enzymes, as a result, this process triggers autophagy. In animal experiments, when combined with rifampicin, ADEP4 has demonstrated anti-biofilm properties and the ability to clear infections [274]. Nevertheless, Nevertheless, the absence of the ClpP protein in certain cells and the easy spread of ADEP4-resistant strains limits its application. Its clinical efficacy in the treatment of PJI remains to be fully explored.

Beyond these strategies, recent research has explored the potential of certain anticancer drugs in combating persister cells. Agents such as mitomycin C and cisplatin have exhibited broad-spectrum bactericidal activity against persister cells, including common biofilm pathogens like *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [275]. In experiments targeting *Pseudomonas aeruginosa* persister cells, cisplatin demonstrated superior bactericidal efficacy compared to mitomycin C [276]. Clinically, 5-fluorouracil has already been utilized to prevent biofilm formation on central venous catheters [277]. Although anticancer agents including mitomycin C and cisplatin have exhibited antibacterial efficacy in vitro biofilm treatment, their clinical translation is hindered by challenges such as significant systemic toxicity. Development of localized delivery strategies, such as surface coatings and topical formulations, is required to mitigate these risks [276, 278].

Immunotherapy

Monoclonal antibodies in immunotherapy tackle biofilm infections through multiple mechanisms [279]. During the early phase of biofilm formation, these antibodies target bacterial surface adhesins, such as ClfA and FnBPA from the MSCRAMMs family. By blocking the binding of

bacteria to fibrinogen, they prevent bacterial attachment, thereby hampering the initiation of biofilm formation [280–282]. In the maturation stage of the biofilm, monoclonal antibodies can target surface proteins involved in intercellular adhesion. For example, antibodies against the Aap protein of *Staphylococcus* epidermidis and the SasG protein of *Staphylococcus aureus* impede intercellular connections and disrupt the construction of the biofilm's three-dimensional structure [283–285]. For established biofilms, monoclonal antibodies that target the stabilizing proteins of the biofilm matrix can promote biofilm dispersion. The anti-DNABII family protein antibody, for instance, destabilizes the biofilm matrix, releasing bacteria from the biofilm and facilitating their clearance by the immune system [286, 287]. Additionally, monoclonal antibodies can neutralize bacterial toxins. Antibodies against toxins like Hla and LukAB, for example, reduce the damage inflicted on immune cells and enhance the ability of immune cells to eliminate the biofilm [288–290]. In conclusion, the multi-stage intervention of monoclonal antibodies in biofilm infection treatment offers a crucial direction for immunotherapeutic strategies against such infections.

Polyclonal antibodies also show great promise in biofilm infection therapy research. In the field of PJI research, the bacterial surface protein SesC is expressed in both biofilm and planktonic bacteria. In vitro experiments have demonstrated that polyclonal rabbit serum targeting SesC can both prevent the formation of *Staphylococcus* epidermidis biofilms and disrupt established ones [291, 292]. In a mouse catheter-associated infection model study, researchers found that a polyclonal anti-SesC antibody effectively reduced biofilm formation [291]. These findings suggest that SesC plays a pivotal role in biofilm formation and is a potential therapeutic target for biofilm-associated infections. Although studies of SesC in PJI models are yet to be conducted, based on its performance in in vitro experiments and the mouse catheter-associated infection model, it is suggested to have potential applications in PJI treatment.

Phage therapy

Phages are a class of viruses that specialize in infecting bacterial cells and were first discovered about 100 years ago, but their development as therapeutic agents was inhibited in the 1930–1940 s by the emergence and widespread use of antibiotics. Phages can produce endolysin and EPS depolymerization enzymes to disrupt the EPS matrix of biofilm, and at the same time, it can accurately recognize bacterial surface proteins, invade into the interior of bacterial cells, and lyse the bacteria by using their own mechanism, which can kill bacteria in different metabolic states and have no effect on human cells, making it a potential therapeutic agent for the treatment of biofilm-associated bacteria [293–295]. Currently, several studies have shown [296–299] that phages can significantly reduce the bacterial population and biofilm volume when used in combination with antibiotics to treat biofilm infections, providing a reference for phage therapy for PJI.

However, phage therapy has limitations. Because each phage is highly specific for a particular bacterial strain, when dealing with mixed infections, phage cocktail therapy is often required for treatment. In a recent study of 33 patients with PJI [300], phage cocktail therapy was shown to be effective. Additionally, in vivo studies involving clinical cases have consistently combined phage therapy with SAT [301, 302]. Therefore, the independent efficacy of phage therapy in clinical practice remains unconfirmed, and further validation is warranted to establish its therapeutic role.

Biofilm-targeted intervention therapies

Enzyme therapy is a promising approach for treating biofilms in PJI. It primarily aids other antimicrobial agents in killing biofilms by degrading extracellular polymers within the biofilm extracellular matrix(ECM).

The biofilm extracellular polysaccharide poly-N-acetylglucosamine(PNAG) is pivotal in biofilm formation and accumulation, making it a prime target for developing biofilm-resistant biomaterials [303, 304]. In vitro studies [305, 306] have shown that dispase B acts on PNAG, nearly killing biofilms completely. When combined with antibiotics, it synergistically enhances the antimicrobial effect. Protease K, an extracellular serine protease produced by *Staphylococcus aureus*, maintains stability across various pH values, high temperatures, and detergent environments. It promotes the separation of *staphylococcal* biofilms containing PNAG and teichoic acid(TA) from infected orthopedic prostheses. This increases bacterial exposure, potentiating the efficacy of antimicrobial therapy and improving treatment outcomes for PJI [307, 308].

Deoxyribonuclease 1(DNase 1) disrupts biofilms by degrading extracellular bacterial DNA(eDNA), a major component of the ECM. In vitro experiments have demonstrated its effectiveness against newly formed biofilms, yet its impact on mature biofilms remains limited. However, when used in conjunction with other antimicrobial agents, DNase 1 shows enhanced ability to remove mature biofilms [309, 310].

D-amino acids, as non-toxic isomers, are involved in bacterial biofilm decomposition. They can integrate into the bacterial cell wall, disrupt amyloid fibrils, inhibit bacterial adhesion, and interfere with biofilm assembly, and have effects at multiple stages of biofilm formation [311, 312]. An in vitro study revealed that D-amino acids, when combined with photothermal hydrogel, completely

cleared mature S. aureus biofilms grown on 3D-printed Ti-6Al-4 V alloy implants. This finding offers valuable insights for the development of new antimicrobial therapeutic strategies [313, 314].

Ultrasound

Ultrasound, an emerging technology, has garnered increasing attention in the diagnosis and treatment of PJI, demonstrating unique value in clinical practice.

In terms of diagnosis, Tunney et al. [315]. first reported in 1998 that low-frequency(20–40 kHz) ultrasound disrupts biofilms on implant surfaces via cavitation, thereby enhancing pathogen positive culture rates in PJI patients. Subsequent studies have progressively validated the diagnostic utility of this technique [316–318], which was incorporated into international consensus diagnostic guidelines by 2021 [105]. However, the absence of standardized optimal ultrasound parameters currently compromises the result comparability and reliability, warranting additional high-quality, multicenter studies to solidify these findings.

In terms of treatment, low-intensity ultrasound combined with antibiotics has been shown to effectively reduce bacterial loads, while high-intensity ultrasound demonstrates efficacy in eliminating bacterial biofilms. A recent study found that non-contact low-frequency ultrasonic debridement(NLFUD) achieved effective infection control in the treatment of one-stage revision PJI without associated complications [319]. In a rabbit model experiment, gentamicin combined with pulsed ultrasound for 72 h led to a significant reduction in E. coli biofilms [320]. Similarly, the combination of ultrasound and vancomycin for treating *Staphylococcus* epidermidis infections significantly decreased the number of viable bacteria on polyethylene discs after 48 h [321]. In vitro studies have also confirmed the synergistic effect of low-intensity ultrasound combined with antibiotics in removing biofilms of Streptococcus epidermidis, *Staphylococcus aureus*, Pseudomonas aeruginosa, and Escherichia coli. Moreover, compared with high-intensity ultrasound for sterilization, low-intensity ultrasound does not increase the risk of microfracture and hematoma formation [322, 323]. Currently, high-intensity ultrasound has shown potential for biofilm infection therapy [324], but the parameters for achieving maximum sterilization and safety in the treatment of PJI still need to be explored in depth. At the same time, the optimal combination of ultrasound debridement with antibiotics and surgical treatment needs to be further investigated to improve treatment outcomes.

In summary, ultrasound technology has great potential for application in the diagnosis and treatment of PJI, but there are still some limitations that require further research and optimization.

Electrochemical methods

Electrochemical methods offer an effective approach to eliminating bacteria from metal surfaces. By applying an electric current to conductive materials like titanium, these methods release hydrogen or hydroxide plasma, triggering electrochemical reactions that disrupt the bacterial environment and physiological processes [325].

Take titanium implants as an example. When a -1.8 V cathodic voltage is applied for electrical stimulation control, the titanium surface accumulates negative charges. Given that most bacteria also have negatively charged surfaces, the resulting electrostatic repulsion—based on the principle of like-charge repulsion—hinders bacterial adhesion to the titanium surface. This mechanism significantly reduces the probability of biofilm formation and subsequent infection.

Other electrochemical techniques, including electrochemical scaffolds [326], electric current applications [327], and electrothermal therapy [328, 329], have demonstrated the ability to reduce environmental bacterial loads. When combined with antibiotics, they show a synergistic bactericidal effect. In the context of escalating antimicrobial resistance, electrochemical methods hold substantial development potential. With continued research, they are expected to bring significant breakthroughs to the treatment of biofilm infections in the future.

Implant surface modification

Implant surface modification is an important strategy to reduce PJI. It aims to optimize implant properties, prevent bacterial adhesion and proliferation, reduce biofilm formation, and thus reduce the probability of infection while ensuring good biocompatibility and function.

Nanoparticles

Nanoparticles offer significant advantages in the prevention and treatment of PJI. They reduce the risk of infection on the implant surface by disrupting bacterial cell membranes, interfering with cellular metabolism, and inhibiting biofilm formation, representing a crucial direction for future prosthesis design [330–332].

The silver ion(Ag+) coating stands out as one of the most effective antibacterial coatings. Among antibacterial metals, silver exhibits the highest antibacterial activity [333]. Silver ions penetrate bacterial cells and attach to the sulfhydryl groups of DNA and metabolic enzymes, thereby impeding bacterial metabolic activity and replication processes, and exerting an antibacterial effect [334]. Research has demonstrated that implants coated with silver nanoparticles(AgNPs) exhibit potent antibacterial properties against common pathogens, including *Staphylococcus aureus*, *Escherichia coli*, and MRSA [335, 336]. Similarly, a clinical study showed that implants coated

with hydroxyapatite containing silver oxide significantly improved postoperative patient function, with no significant toxicity of Ag + to the human body observed [61, 62]. Notably, the variations in total silver loading, release kinetics, and preparation processes exist among different types of silver coatings, which in turn result in differences in clinical efficacy and safety [337]. Patients are at risk of argyria, and studies have suggested that minimizing the total dosage of silver coatings and controlling the release rate are key to reducing toxicity [337, 338]. Currently, the majority of silver coatings fail to cover the joint surface or bone contact area. Only the Kyocera coating achieves uniform silver loading on the contact surface via a hydroxyapatite carrier, balancing antimicrobial activity with osseoconductivity. However, the long-term efficacy of this coating remains to be validated [61, 337, 339]. At present, insufficient evidence exists to support or refute the application of silver coatings in PJI, and further research is required to confirm their clinical efficacy.

In recent years, new antimicrobial coating technologies have emerged. Studies indicate that iodine-coated titanium implants strongly inhibit biofilm-forming bacteria such as MRSA, *Pseudomonas aeruginosa*, and *Staphylococcus* epidermidis, with no viable bacteria detectable on their surfaces [340, 341]. Copper ion coatings directly contact bacteria, suppressing biofilm formation and killing bacteria. Applying copper ion coatings to medical device surfaces significantly reduces the adhesion and growth of pathogens like *Staphylococcus aureus* [342]. Selenium nanoparticle coatings not only prevent the formation of MRSA and *Staphylococcus* epidermidis biofilms on implants but also promote osteoblast proliferation and differentiation, facilitating implant-bone integration and reducing the risk of prosthesis loosening [343, 344]. Additionally, zinc oxide nanoparticles display inhibitory activity against various bacteria, and zinc-coated titanium has shown osteogenic potential, showing great potential for implant surface modification [345, 346]. Composite nanoparticle coatings, which combine silver nanoparticles with other antibacterial or bone-integration-promoting materials, can achieve both high antibacterial efficacy and excellent biocompatibility [347].

Despite the promising prospects of nanoparticles, they still face challenges in practical application. The long-term biosafety of nanoparticles, precise control over nanoparticle synthesis, release, and the optimal loading amount on implant surfaces require further investigation. With continued research, it is expected that nanoparticles will pave the way for new directions for preventing and treating PJI.

The defensive antimicrobial coating

Defensive antimicrobial coating(DAC) comprises hyaluronic acid and polylactic acid, categorized as biodegradable polymer hydrogel systems, and is utilized for PJI prevention/treatment via antibiotic incorporation [348]. In vitro investigations have revealed that antibiotic-loaded DAC hydrogel completes drug release within 96 h, significantly inhibiting bacterial colonization and biofilm formation, with an 80% retention rate post-implantation [349]. A multicenter prospective randomized clinical trial confirmed that antibiotic-loaded DAC reduced postoperative infection rates from 6–0.6%($P = 0.003$), without compromising osseointegration, and no local/systemic adverse reactions were observed [350]. Consistent with prior findings, multiple studies have also demonstrated the safe and effective reduction of PJI risk by antibiotic-loaded DAC [351–353].

In summary, DAC loaded with antibiotics emerges as a promising strategy for PJI management. However, its widespread clinical translation requires further optimization of coating retention technology, screening of optimal antibiotic combinations, and validation by additional high-quality clinical investigations.

Other coatings

Nitric oxide(NO) plays a crucial role in preventing biofilm formation by precisely regulating the c-di-GMP levels within *Pseudomonas aeruginosa* [354]. Due to the intrinsically unstable characteristic of NO, researchers have engineered a near-infrared light-responsive hydrogel system to enable controlled NO release. The NO free radicals released from the fabricated coating show strong anti-biofilm activity, with an antibacterial rate reaching over 92% [355]. In vitro studies have shown that the NO-releasing titanium coating for orthopedic implants not only exhibits remarkable antibacterial effectiveness but also poses minimal toxicity to human primary osteoblasts [356]. The use of NO in implant coatings integrates high antibacterial performance and strong biosafety, offering extensive application potential in orthopedic implants. This approach is expected to bring about substantial advancements in the prevention and treatment of implant-associated infections.

Chitosan, a natural biopolymer well-known for its antibacterial characteristics, has attracted significant attention in the prevention and treatment of PJI. As a cationic polymer, chitosan can bind to the negatively charged bacterial cell walls. This interaction causes structural damage to the cells and disrupts DNA and RNA synthesis. Consequently, chitosan exhibits broad-spectrum antibacterial activity and has a low potential for inducing drug resistance [357, 358]. Unlike most antibacterial materials, chitosan exhibits dual functionality. It can not only suppress bacterial growth but also enhance osteoblast activity. In vitro studies have demonstrated that chitosan-hyaluronic acid composite coatings on titanium surfaces can concurrently inhibit bacterial adhesion and promote osteoblast

proliferation [359]. Due to its outstanding biocompatibility, chitosan has significant potential for clinical applications. Currently, while large-scale clinical trials are still scarce, the robust findings from in vitro experiments and animal studies provide substantial evidence for its transition to clinical practice. To facilitate its future clinical implementation, additional research is required to evaluate its long-term stability and identify the optimal dosage.

Antimicrobial peptides(AMPs), which are effector proteins naturally synthesized by organisms and widely present across various species, exert antibacterial effects through multiple mechanisms. These mechanisms involve disrupting bacterial cell membranes, interfering with intracellular metabolic pathways, and binding to specific bacterial targets. Their distinctive action modes reduce the probability of inducing bacterial resistance. In the research domain of joint prostheses, AMP-based coatings have emerged as a key area of investigation. For instance, titanium implants modified with GL13K, an antimicrobial peptide derived from the parotid gland, demonstrate both bactericidal and antibacterial activities [360]. Moreover, the ponericin G1-based antimicrobial peptide polymer film coating, fabricated using layer-by-layer assembly technology, effectively inhibits bacterial adhesion and biofilm formation [361]. However, AMPs currently encounter several obstacles. High production costs, low in-vivo stability, and insufficient clinical validation are major concerns. To promote their clinical application in the treatment of PJI, future efforts should focus on developing efficient production methods, improving stability, and accelerating clinical trials.

Local antimicrobial drug delivery system

Articular cavity delivery

Articular cavity delivery is a pivotal method within local antimicrobial drug delivery systems. Antimicrobial-loaded microparticles or nanocapsules are directly implanted into the joint cavity, enabling the local sustained release of these agents. This approach effectively improves therapeutic results while reducing systemic adverse reactions.

For example, daptomycin-loaded polycaprolactone(PCL) microparticles demonstrate enhanced antibacterial and anti-biofilm capabilities compared to vancomycin-loaded counterparts, positioning them as viable options for treating Gram-positive bacterial biofilm infections [362]. In vitro research has shown that silver titanium dioxide-containing nanocapsules exhibit antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*, coupled with excellent biocompatibility, indicating their potential as materials for antimicrobial drug delivery systems [363]. Microparticle/nanocapsule delivery systems warrant further investigation.

Calcium sulfate(CS) functions as a biodegradable antibiotic delivery carrier, enabling complete release of loaded antibiotics with sustained elution over weeks [364]. While studies have demonstrated its capacity for high-concentration local antibiotic release to inhibit/eradicate biofilms and control infections [365, 366], other studies have indicated that its efficacy is limited [367, 368] and reported risks such as wound exudation, heterotopic ossification, or hypercalcemia(albeit with low incidence) [369, 370]. Current evidence for CS efficacy in PJI remains insufficient, marked by a paucity of high-quality controlled studies. Although promising, its routine clinical application warrants caution until further research validates efficacy and balances costs/risks.

Local antibiotic depot

Calcium hydroxyapatite (CHA), a calcium phosphate-based antibiotic delivery carrier with a porous structure, combines osteoconductive properties and sustained antibiotic release capabilities, making it particularly suitable for the management of cavitary bone defects suspected of osteitis. Its isothermal hardening properties protect antibiotics from thermal damage, but slow/incomplete degradation may lead to uneven drug release and increased bacterial colonization risk [369]. Studies have shown that CHA demonstrates high success rates, sustained efficacy, and functional recovery in PJI treatment, with proven safety, particularly for complex cases [371, 372]. The CHA-CS composite delivery carrier combines CS's rapid drug release with CHA's osteogenic ability for synergistic effects [369]. For instance, in vitro experiments with Cerament®(40% CHA + 60% CS) have shown biofilm inhibition and prosthesis stability enhancement [373], while clinical studies report maintenance of high local antibiotic concentrations, though postoperative drainage may reduce drug utilization [374]. PerOssal®(51.5% nanocrystalline CHA + 48.5% CS) used with bone cement spacers in knee PJI rapidly reduces CRP and shortens reimplantation interval, but efficacy requires validation in large-scale trials [375]. Despite therapeutic potential, composite delivery carriers lack robust clinical evidence and require high-quality studies for validation.

Bone cement optimization

Antibiotic-loaded bone cement is extensively applied in joint replacement surgeries. Nevertheless, traditional bone cement is plagued by restricted antibiotic release, sluggish release profiles, and subpar therapeutic results, thereby highlighting the urgency of developing advanced delivery materials.

Studies have indicated that the incorporation of sodium alginate and polyhydroxybutyrate-hydroxyvalerate (PHBV) microparticles encapsulating rifampicin into bone cement not only preserves the material's desirable

mechanical properties but also enhances its antibacterial efficacy. These composite cements have shown effectiveness in both in vitro and in vivo investigations [376]. Moreover, mesoporous silica nanoparticles(MSN) can efficiently boost drug release rates while maintaining the mechanical strength of bone cement. MSN can also be used to fabricate binary delivery systems with efficient drug delivery and low cytotoxicity, presenting significant potential for the development of high-performance antibiotic bone cements [377].

In summary, microparticles and nanocapsules are promising candidates for further investigation as novel delivery materials. Future research endeavors should prioritize accelerating their development to promote the clinical translation of antibacterial delivery materials for articular cavity applications and bone cement formulations, ultimately enhancing patient treatment outcomes.

Vaccines

Vaccines provide a promising strategy for the prevention of PJI. By eliciting targeted immune responses against specific pathogens, they have attracted substantial interest in recent years.

Animal studies have shown that vaccines using IsdB as an antigen possess strong immunogenicity and offer significant protection against *Staphylococcus aureus* infections [378]. In a rabbit model, a separate study demonstrated that the combination of vaccination and antibiotic treatment effectively eradicated biofilm infections caused by MRSA. These results highlight the potential of vaccines as preventive strategies and indicate their feasibility for further development as immunotherapeutic agents [379]. Recently, Wang et al. [380] developed a vaccine with the E2 subunit of the pyruvate dehydrogenase complex(PDHC) as the antigen. In a murine model, this vaccine induced a robust protective immune response against S. aureus strains, suggesting that PDHC is a promising candidate for tackling MRSA infections. Despite these promising preclinical findings, the development of preventive vaccines has encountered significant hurdles. Multiple clinical trials of vaccines designed to target *Staphylococcus aureus* and coagulase-negative *staphylococci* have been terminated prematurely due to insufficient evidence of efficacy. In certain instances, these trials even reported increased mortality rates among vaccine recipients [381]. To date, no human clinical trial of such vaccines has yielded successful outcomes, this disparity is presumably due to the inherent differences between human and animal immune responses [381].

Currently, vaccine research and development face the challenge of transforming from animal experiments to human applications. In the future, we need to conduct in-depth research on the human immune response mechanism and build an experimental model that is closer to the human immune response, to improve the effectiveness and safety of vaccines for humans.

Machine learning models

Machine learning algorithms analyze extensive real-world datasets including patient demographics, medical histories, imaging findings, treatment approaches, and clinical outcomes to identify patterns. These patterns can be applied across different phases of TJA and PJI. This technology enables clinicians to identify infection risk factors, support treatment decision-making, predict the optimal implant size, and forecast treatment efficacy and the risk of reinfection after PJI revision surgery. As new data become available, machine learning models can be iteratively improved, enhancing their clinical results [382–385].

It is important to note that these models are currently in the research stage. Before widespread clinical implementation, additional robust clinical evidence is required to validate their potential benefits.

Conclusion

The management of PJI remains a significant challenge in orthopedic surgery, which warrants focused attention. The prevention of PJI holds paramount priority and should be integrated throughout the perioperative period. Preoperatively, patient risk factors should be optimized(such as HbA1c ≤ 7.0% and correction of malnutrition), with implementation of nasal mupirocin combined with chlorhexidine bathing for decolonization, and administration of single-dose antibiotic prophylaxis 1 h prior to surgery. Intraoperatively, strict aseptic techniques should be adhered to, surgical duration optimized, the wound irrigated with povidone-iodine solution before closure, drainage placement determined based on individual patient factors, and watertight closure achieved via layered sutures with barbed sutures. Postoperatively, silver-ion dressings are applied, and antibiotic therapy may be extended in high-risk cases. Although diagnostic criteria for PJI have undergone multiple updates, the 2011 MSIS criteria remain the most widely adopted, requiring comprehensive evaluation of laboratory, pathological, and imaging examinations for diagnosis. Laboratory evaluations include serum biomarkers(most commonly CRP, ESR, WBC), synovial fluid biomarkers(e.g., AD, calprotectin, and LE demonstrate high diagnostic value, while WBC and PMN% retain irreplaceable roles), and ultrasound-assisted microbial culture to enhance detection rates. Pathological examination(including preoperative biopsy, intraoperative frozen section biopsy, and postoperative histopathological examination) serves as one of the gold standards. The 2021 EBJIS consensus has incorporated NM imaging, particularly useful for

differentiating cases refractory to conventional examinations, positioning it as an exclusion tool for chronic PJI. PJI treatment necessitates combined antibiotic and surgical interventions. Antibiotic therapy includes empirical treatment after diagnosis, targeted therapy following pathogen identification, and SAT for non-surgical candidates. Surgical options comprise DAIR, one-stage/two-stage revision, and salvage procedures. Implementation of standardized infection prevention protocols, rational antibiotic use, surgical technical innovations, and advancements in biomaterials have contributed to a reduction in PJI incidence. However, the spread of bacterial resistance and transmission of multidrug-resistant organisms in healthcare settings pose new challenges for PJI prevention and treatment.

Future perspectives should focus on the development of novel antibiotics and drugs targeting persister cells, exploration of immunotherapies(e.g., monoclonal/multiclonal antibodies) and phage cocktail therapy, and development of ultrasound and electrochemical-based antibacterial technologies. Optimization of antibacterial-coated implants(e.g., silver ions) and local drug delivery systems, advancement of vaccine development, and application of machine learning models for infection risk prediction are also imperative. Multidisciplinary integration is essential to overcome the management challenges of PJI.

Author contributions

X.H. X, J.N. X, and B. Z contributed equally to this work. X.H. X, J.N. X, and B. Z conducted the literature review, synthesized the research findings, and wrote the main manuscript text. M.Y. L and J.J. G assisted in literature collation, key content verification, and reference validation. Q. B, Q.F. Y, and J. Z provided critical guidance, revised the manuscript, and ensured its scientific accuracy. All authors reviewed the manuscript and approved the final version for submission.

Funding

1.National Natural Science Foundation of China(No. 82460423 to Dr. Jun Zhang).
2.Guizhou Provincial Office of Science and Technology(Qiankehe Major [2025] 010 to Dr. Jun Zhang)
3.Zhejiang Administration of Traditional Chinese Medicine(GZY-ZJ-KJ-23057 to Dr. Jun Zhang).
4.Bijie Science and Technology Bureau(BKH [2023] No. 55 to Dr. Jun Zhang)
5.Guizhou Provincial Administration of Traditional Chinese Medicine(QZYY-2024-109 to Dr. Jun Zhang).
6.Guizhou Provincial Office of Science and Technology(Qiankehe Foundation-[2024] Youth 385 to Dr. Jun Zhang)
7.Health Commission of Guizhou Province(gzwkj2024-159 to Dr. Jun Zhang).
8.Hangzhou Medical College(KYYB2023008 to Dr. Jun Zhang).
9.Guizhou Provincial Office of Science and Technology(Qiankehe LC(2025) general to Dr. Jun Zhang).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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Received: 1 May 2025 / Accepted: 26 August 2025
Published online: 26 September 2025

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