



Review Article

Microbiological Diagnosis of Periprosthetic Infections: Overview of the Main Microbial Pathogens

Andrei Vladimirovich Kozlov¹, Artem Viktorovich Lyamin¹, Araik Levikovich Misakyan¹, Aleksei Alekseevich Neilenko¹*, Dmitry Sergeevich Kudashev² and Maria Yur'yevna Sefedinova³

¹Professional Center for Education and Research in Genetic and Laboratory Technologies, Samara State Medical University, Samara, Russia; ²Department of Traumatology, Orthopedics and Extreme Surgery named after Academician of the Russian Academy of Sciences A.F. Krasnov, Samara State Medical University, Samara, Russia; ³Department of General Surgery and Surgical Diseases, Samara State Medical University, Samara, Russia.

Abstract | Annual expenses for treatment of periprosthetic infections (PPIs) in the United States exceed \$ 8.6 billion, and in Europe they amount to about 2 billion euros, where the 5-year mortality rate is 26%. PPIs occur in 0.3-2.2% of cases with primary prosthetics, while recurrent periprosthetic infections occur in 23.2-31.5% of cases. The occurrence of PPIs after prosthetics is a rare phenomenon, however, this complication, if it occurs, requires hospitalization of the patient, long-term antibiotic treatment and, possibly, surgical intervention. The diagnosis of PPIs is established on the basis of clinical data, and laboratory and instrumental studies. Effectiveness of treatment directly depends on the rate of pathogen detection and its sensitivity to antimicrobial drugs. The article focuses on bacterial and fungal pathogens of PPIs, and discusses the features of laboratory diagnostics, including microbiological cultivation, polymerase chain reaction, and next-generation sequencing in the context of PPIs diagnostics. The aim of the study is to analyze the structure of the causative agents of PPIs.

Received | October 15, 2025; **Revised** | November 10, 2025; **Accepted** | November, 17 2025; **Published** | December 02, 2025

***Correspondence** | Aleksei Alekseevich Neilenko, Professional Center for Education and Research in Genetic and Laboratory Technologies, Samara State Medical University, Samara, Russia; **Email:** lesha.neylenko@mail.ru

Citation | Kozlov, A.V., A.V. Lyamin, A.L. Misakyan, A.A. Neilenko, D.S. Kudashev and M.Y. Sefedinova. 2025. Microbiological diagnosis of periprosthetic infections: Overview of the main microbial pathogens. *Novel Research in Microbiology Journal*, 9(6): 454-469.

DOI | <https://dx.doi.org/10.17582/journal.nrmj/2025/9.6.454.469>

Keywords | Periprosthetic infection, Infections related to prosthetics, Prosthetics, Prosthetics complication



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Introduction

The number of periprosthetic infections (PPIs) continues to grow steadily due to increase in the number of prosthetic joints (Izakovicova *et al.*, 2019; Ashkenazi *et al.*, 2023). By 2030, the number of hip and knee replacements is expected to increase by 174%. 673%, respectively (Bi *et al.*, 2019; Flynn *et al.*, 2024). Annual expenses for treatment of PPIs in the

United States exceed \$ 8.6 billion, and in Europe they amount to about 2 billion euros (Sukeik and Haddad, 2019; Barros *et al.*, 2022; Sarantis *et al.*, 2022). The average total cost of revision for total knee arthroplasty associated with PPIs is 75 thousand dollars (Leta *et al.*, 2024). The average age of patients with PPIs is 60-66 years, and the 5-year mortality rate is 26% (Ivantsov *et al.*, 2020; Nikolaev *et al.*, 2021; Karczewski *et al.*, 2023; Piuzzi *et al.*, 2024). PPIs occur in 0.3-2.2% of cases

with primary prosthetics, while recurrent PPIs occur in 23.2–31.5% of cases (Dobrovolskaya *et al.*, 2020). The objective of this study is to analyze the structure of the causative agents of periprosthetic infections.

Elderly people are most often susceptible to the occurrence of PPIs in presence of diseases leading to a decrease in bone strength and/or with a comorbid background (Flurin *et al.*, 2019; Izakovicova *et al.*, 2019; Karczewski *et al.*, 2023). Risk factors for PPI include: *Rheumatoid arthritis*, diabetes mellitus, obesity and a history of multiple surgeries, post-traumatic osteoarthritis, prolonged use of immunosuppressores, and prolonged hospital stay, leading to the appearance of resistant microflora and subsequently to complications such as sepsis, systemic inflammatory reactions syndrome, and pulmonary embolism (Stewart and Bjarnsholt, 2020; Onorato *et al.*, 2024). In addition, the risk of systemic inflammation increases with PPIs, if a substantial period of time has passed since the onset of inflammation (Izakovicova *et al.*, 2019). Occurrence of PPI requires an integrated approach to the diagnosis and treatment of this disease with the participation of physicians of various specialties (Izakovicova *et al.*, 2019).

Periprosthetic infections are caused by various types of microorganisms. The Gram-positive bacteria are the most common, while Gram-negative microorganisms are much less common, however, the infections caused by them are characterized by difficult treatments and unfavorable outcomes. In addition, PPIs caused by Gram-negative bacteria are more common in the form of mixed infections (Dandé *et al.*, 2021; Tsiskarashvili *et al.*, 2022). The epidemiology of pathogens differs in prosthetics of different joints (Flurin *et al.*, 2019).

According to the TSUKAYAMA classification, PPIs are divided into 4 groups depending on the time of development; mainly (1) early acute, (2) early acute delayed, (3) late chronic, and (4) acute hematogenous infections (Flurin *et al.*, 2019). The various types of PPI differ from each other in the main pathogens and the mechanism of infection; accordingly, the clinical course is extremely important for the clinician to take into account during treatment (Fink *et al.*, 2019). Early acute ones occur within 4 weeks after prosthetics, late chronic ones after 4 weeks, and acute hematogenic ones occur after a year or more (Tsukayama *et al.*, 1996; Murylev *et al.*, 2022).

Pathogenesis

There are several mechanisms for penetration of microorganisms to the surface of prostheses. Firstly, wound contamination is possible during injury or during surgery, which usually leads to early and acute delayed infection (Renz *et al.*, 2019). Secondly, there is a possibility of hematogenous and lymphogenic spread of the pathogen from foci of acute and chronic infection located in the respiratory tract, on the skin, soft tissues, the gastrointestinal tract, and the genitourinary system (Barros *et al.*, 2022; Izakovicova *et al.*, 2019). For example, in patients with caries and inflammatory diseases of the oral tissues caused by bacterial pathogens, the probability of occurrence of PPIs one year after prosthetics is 1.6 times higher than patients without caries (Gordon *et al.*, 2024). Hematogenous spread is possible with daily oral hygiene, dysbiosis, and concomitant increased intestinal permeability, leading to the creation of a Trojan horse of phagocytic cells and bacteria that can penetrate to the joints (Charlotte Höfer *et al.*, 2022; Piuzzi *et al.*, 2024).

After penetration to the prosthesis, microorganisms need to gain a foothold on the surface. In turn, the following types of adhesion are distinguished, including passive reversible adhesion due to non-specific forces (*i.e.*, electrostatic and acid-base interaction), active irreversible specific interaction of microorganisms, and soluble proteins trapped on the surface of the prosthesis. Later, some microorganisms form biofilms, which reduce the effectiveness of antibacterial treatment by 1000 times (Khatoon *et al.*, 2018). The following microorganisms most often produce biofilms: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., *Cutibacterium acnes*, *Candida albicans*, *C. parapsilosis*, *C. glabrata*, and *C. tropicalis* (Rienmüller and Borens, 2016). It should be emphasized that biofilms affect the host's immune response; therefore, PPI can be considered as an immune dysregulation of the body. In addition, the process of horizontal gene transfer is much more active in biofilms, contributing to the widespread spread of antibiotic resistance (Arciola *et al.*, 2018; Piuzzi *et al.*, 2024).

Periprosthetic infection is a consequence of complex interaction among the implant, the microorganism, and the human body (Arciola *et al.*, 2018). Not only microbial pathogens, but also prosthesis material itself

is capable of causing local tissue reactions, including acute and chronic inflammation, granulation tissue formation, and fibrous encapsulation (Arciola *et al.*, 2018; Izakovicova *et al.*, 2019). The prosthesis material reduces local immunity, leading to an increased risk of developing PPIs (Arciola *et al.*, 2018; Izakovicova *et al.*, 2019). Colonization of the lacunar-canalicular network of osteocytes by microorganisms leads to long-term persistence, due to inaccessibility of this histological barrier to the immune system and antibiotics (de Mesy Bentley *et al.*, 2017; Piuze *et al.*, 2024).

The inflammatory process leads to the loss of a stable connection between the prosthesis and bone tissue and its failure, which requires one or more operations, including arthrodesis, amputation, exarticulation, and lethal outcomes are also possible (Gazendam *et al.*, 2022; Gramlich and Parvizi, 2023).

Laboratory diagnostics of microorganisms

Identification of the pathogen is crucial for selecting the necessary treatment and prognosis for the patient (Gazendam *et al.*, 2022). The cultural method is the gold standard in the diagnosis of PPI, but is characterized by a number of serious drawbacks (Azad *et al.*, 2022). Firstly, isolation of the pathogen from a biofilm and bone tissue is complicated. Secondly, the culture method is characterized by low sensitivity. Thirdly, preoperative antibiotic therapy can affect the viability of microorganisms. Fourthly, traditional cultivation methods depend on the ability of bacteria to grow in a certain nutrient medium, so the proportion of PPIs with a negative result is about 40% (Gazendam *et al.*, 2022; Tsikopoulos and Meroni, 2023). The timing of results is also important, which can take up to 2 weeks for seeding (Portillo and Sancho, 2023). The seeding material is preoperative synovial fluid samples, surgical materials, dispersed hard tissues, and samples obtained as a result of ultrasound treatment of prostheses (Vrancianu *et al.*, 2023). In order to increase sensitivity and specificity, cultivation in commercial vials for hemocultures is possible (Li *et al.*, 2019). The combined sensitivity of preoperative fluid, intraoperative tissue, and ultrasound fluid for the diagnosis of PPI are 0.63 (95%; 0.56–0.70), 0.71 (95%; 0.63–0.79), and 0.78 (95%; 0.68–0.85), whereas the specificity is 0.96 (95%; 0.93–0.98), 0.92 (95%; 0.86–0.96), and 0.91 (95%; 0.83–0.95), respectively (Watanabe *et al.*, 2024). When using vials for hemocultures, the combined

sensitivity is 0.70 (95%; 0.66–0.75), while specificity is 0.97 (95%; 0.95–0.98) (Li *et al.*, 2019).

The indisputable advantage of this technique is the possibility of setting up phenotypic assays for antibiotics, and detecting small-colonial forms of bacteria that are common in chronic infections and require the appointment of intracellular antibiotics, which is impossible upon using the molecular genetic methods (Portillo and Sancho, 2023).

In an attempt to increase the accuracy of diagnosis, molecular genetic variants of pathogen identification have been proposed, namely various new generation sequencing and polymerase chain reaction (PCR) methods (Azad *et al.*, 2022). PCR methods are divided into universal PCR, necessary for the detection of genes ubiquitously present in microorganisms, specific PCR; the task of which is to detect a specific microorganism or mechanism of resistance, multiplex PCR, which is performed to simultaneously detect multiple microorganisms and/or resistance mechanisms (Portillo and Sancho, 2023). Universal PCR without additional methods indicates only the presence of microorganisms, without precise species identification (Tkadlec *et al.*, 2019). The results of sensitivity and specificity of different PCR methods differ considerably in different studies (Li *et al.*, 2022; Subedi *et al.*, 2024). Despite their high sensitivity and specificity, primers in specific PCR tests are single, which makes them difficult to screen for PPIs and limits their use in clinical practice (Higgins *et al.*, 2022; Vrancianu *et al.*, 2023). Multiplex PCR is characterized by its high efficiency, surpassing the results of traditional methods of culturing *Cutibacterium* spp. and coagulase-negative staphylococci; however, the ability to detect only those microorganisms targeted by primers creates problems in identifying rare pathogens (Zhou *et al.*, 2024).

In the case of new generation sequencing (NGS) method, it raises the question of economic feasibility of this analysis, complexity of the formulation, impossibility of determining the sensitivity of a microorganism to antibiotics, and lack of standardization of analysis methods, which substantially limits the possibility of widespread use in routine clinical practice (Portillo and Sancho, 2023). The sensitivity and specificity of NGS method varies very widely depending on nature of the material, preanalytical stage, and method of performing the

analysis (Portillo and Sancho, 2023). The main advantage of molecular genetic techniques is absence of the need for cultivation, which considerably reduces the study time (Auñón *et al.*, 2022).

A common limitation of the aforementioned methods used in detection of mixed infections with draining inflammations is the difficulty of determining clinical significance of the detected microorganisms, since there is no clear understanding of the cause of infection, which turned out to be transient microflora (Arciola *et al.*, 2018). However, diagnosis of chronic PPI is currently an urgent task (Portillo and Sancho, 2023).

Microorganisms causing PPIs

The Staphylococcaceae family

About 50% or more of bacterial infections are caused by *Staphylococcus aureus* and *Staphylococcus epidermidis* (Dobrovol'skaya *et al.*, 2020; Tsiskarashvili *et al.*, 2022). *Staphylococcus aureus* differs from other pathogens as it leads to early onset of the infectious process, early bacteremia, and frequent recurrence (Hersh *et al.*, 2019; Guo *et al.*, 2020; Klasan *et al.*, 2021). There are also other species, including *Staphylococcus capitis*, *Staphylococcus warneri*, *Staphylococcus hominis*, and *Staphylococcus haemolyticus* (Hersh *et al.*, 2019). *Staphylococcus epidermidis* is more likely to cause hip PPI, while *Staphylococcus aureus* causes both knee and hip PPI (Guo *et al.*, 2020; Ivantsov *et al.*, 2020). The resistance of *Staphylococcus epidermidis* and *Staphylococcus aureus* to methicillin increases every year. Moreover, the rates of development of methicillin-resistant *Staphylococcus epidermidis* strains amounted to 89% of the total number of *Staphylococcus epidermidis*. In PPIs, methicillin-resistant *Staphylococcus aureus* (MRSA) predominantly causes early infections, whereas methicillin-sensitive *Staphylococcus aureus* (MSSA) leads to delayed and late infections. The number of MSSA infections is approximately 2.5 times greater than that of MRSA infections (Arciola *et al.*, 2018). These pathogens are highly sensitive to vancomycin, linezolid, amoxiclav, and ceftriaxone (Tsiskarashvili *et al.*, 2022). An important feature characterizing these pathogens is their ability to form biofilms on the surface of the prosthesis (Dobrovol'skaya *et al.*, 2020).

Periprosthetic infections are complicated by the ability of *Staphylococcus* spp. to form L-forms, characterized

by slow growth, an aberrant colony shape, and unusual metabolic characteristics. These are in addition to the possibility of their persistence within phagocytes protected from the immune system of the microorganism and antimicrobial agents (Hersh *et al.*, 2019). A number of scientists believe that it is most appropriate to use a two-stage replacement of the endoprosthesis as a treatment for PPIs (Ivanian *et al.*, 2021). *Staphylococcus aureus* is the common causative agent of PPIs in the United States, while *Staphylococcus epidermidis* is more common in Europe (Arciola *et al.*, 2018).

Staphylococcus epidermidis is characterized by numerous virulence factors. The protein autolysin (AtlE) plays an important role in biofilm formation, which also promotes lysis of host cells and release of extracellular DNA. *Staphylococcus aureus* has a similar protein with a similar function. *Staphylococcus aureus* and *Staphylococcus epidermidis* produce surface proteins able to recognize and bind collagen and fibronectin (Arciola *et al.*, 2018).

The Streptococcaceae family

Periprosthetic infections caused by streptococci account for up to 10% of all cases (Dobrovol'skaya *et al.*, 2020; Tsiskarashvili *et al.*, 2022). The most common pathogenic species include *Streptococcus agalactiae* (34.4%), β -hemolytic streptococci with large colonies (26.2%), the viridans group of streptococci (18.6%), *Streptococcus pyogenes* (7.8%), *Streptococcus anginosus* group (6.9%), *Streptococcus pneumoniae* (4.5%), and other streptococci (1.5%) (Lora-Tamayo *et al.*, 2017). PPIs caused by streptococci occur mainly with the hematogenous spread of infection from the gastrointestinal and genitourinary tracts. *Streptococcus disgalactiae* is mainly detected in the elderly persons (Lora-Tamayo *et al.*, 2017; Erden *et al.*, 2020).

Periprosthetic infections caused by *Streptococcus* bacteria are accompanied by a high percentage of unsuccessful treatment compared to those caused by bacteria of the genus *Staphylococcus*; with the worst treatment results recorded in patients with *Streptococcus agalactiae* compared to other *Streptococcus* spp. There is an assumption that this bacterial pathogen spreads already as part of the biofilm and forms a biofilm faster on surface of the prosthesis. The *Streptococcus agalactiae* capsule that is rich in sialic acid protects the pathogen from phagocytosis. A key factor in the pathogenesis of *Streptococcus agalactiae*

is β -hemolysin, enabling the pathogen to invade epithelial and endothelial cells (Cho *et al.*, 2024).

The Enterococcaceae family

About 2-11% of PPIs are caused by enterococci. Despite low virulence of these pathogens; however, treatment of these infections is complicated by slow bactericidal action of antimicrobial agents and increasing antibiotic resistance (Haeberle *et al.*, 2024; Hersh *et al.*, 2019; Kheir *et al.*, 2017a; Maurille *et al.*, 2023; Renz *et al.*, 2019). *Enterococcus* spp. are often found in combination with other microorganisms of different species in the same sample (Renz *et al.*, 2019; Maurille *et al.*, 2023). The most common pathogens among *Enterococcus* spp. are mainly; *Enterococcus faecalis* (89%), *E. faecium* (9%), and others (2%) (Renz *et al.*, 2019).

Periprosthetic infections caused by *Enterococcus* spp. occurs in 54-55% of cases with hip replacement, 40% of cases with knee replacement, and 3% with elbow and shoulder joint replacement (Hersh *et al.*, 2019; Renz *et al.*, 2019). The intraoperative route of infection is most common (more than 80%); however, hematogenous one is much less common (17%) (Renz *et al.*, 2019).

Enterococcus faecalis is a Gram-positive facultative anaerobic bacterium that occurs in the gastrointestinal tract and is a part of the human microbiota. This pathogen forms a biofilm and causes urinary tract infections (Cho *et al.*, 2024; Haeberle *et al.*, 2024).

The Pasteurellaceae family

PPI caused by *Haemophilus parainfluenzae* or *Pasteurella multocida* is rare because it has low pathogenic activity. *H. parainfluenzae* is a Gram-negative coccoid-like bacterium. This bacterium is a part of the normal microflora of the oral cavity and upper respiratory tract, less often isolated from the mucous membrane of the gastrointestinal tract, vagina, and urethra. However, under certain unfavorable conditions, this pathogen causes pneumonia, endocarditis, and other diseases. In most cases, *H. parainfluenzae* infection is preceded by invasive procedures, including those in the oral cavity (Sermet *et al.*, 2021; Medel-Plaza *et al.*, 2023).

The Mycoplasmataceae family

Representatives of the *Mycoplasmataceae* family are often the cause of lung and genitourinary infections,

rarely lead to PPI; however, there are reported cases of knee and hip arthroplasty (Rieber *et al.*, 2019; Cai *et al.*, 2023). *Ureaplasma urealyticum* and *Ureaplasma parvum* are considered as difficult-to-grow pleomorphic bacteria that colonize mainly the genitourinary tract (Rieber *et al.*, 2019; Muramatsu *et al.*, 2022). An important morphological aspect is that they lack a cell wall, which must be taken into account when prescribing an empirical therapy. These pathogens differ in being difficult to isolate using standard cultivation methods. Gram staining and cultivation on culture plates give negative results; therefore, PCR with the determination of 16S rRNA sequencing is used to identify these pathogens (Rieber *et al.*, 2019; Ball and Snape, 2021).

The Enterobacteriaceae family

The *Enterobacteriaceae* family accounts for about 8% of all PPIs (Zhou *et al.*, 2021; Tsiskarashvili *et al.*, 2022). Among them, *Enterobacter cloacae* accounts for 15.4% of PPIs, *E. coli* (42.6%), and *Klebsiella pneumoniae* (38.5%) (Zhou *et al.*, 2021; Tsiskarashvili *et al.*, 2022).

A recent study revealed that PPI caused by *E. cloacae* is more common after hip replacement than knee one, and has also reported that this pathogen is predominantly polymicrobial in nature, often associated with the family *Staphylococcaceae*, *P. aeruginosa*, *E. faecalis*, and *K. pneumoniae*. Of the 108 PPI cases reported in this study, 12 cases have been associated with *E. cloacae*, and have developed within 3 months after the endoprosthesis (Ashkenazi *et al.*, 2023).

Serratia marcescens, being a Gram-negative anaerobic bacterium, leads to the appearance of PPIs in less than 1% of all reported PPIs cases, usually detected in the respiratory and urinary tracts (Karczewski *et al.*, 2023). According to the literature data, a total of 14 cases of PPIs caused by *S. marcescens* have been described. The average age of patients is 66 years, and 75% of them are men (Karczewski *et al.*, 2023). In four cases, coexistence with *C. glabrata*, *Bacillus cereus*, *Proteus mirabilis*, and *Staphylococcus epidermidis* has been observed. PPI associated with *S. marcescens* is characterized by poor prognosis of the patients as a result of frequent recurrence of infection (Karczewski *et al.*, 2023).

Klebsiella pneumoniae is most often associated with hip joint damage. This pathogen is characterized

by severe course of infections and patients high mortality rate (Cespedes Santana *et al.*, 2022; Fischer *et al.*, 2024). It exists in urinary tract, intra-abdominal, and pneumonia infections (Tosatto *et al.*, 2020). *K. pneumoniae* is considered as a pathogen with a high level of natural resistance (Karczewski *et al.*, 2023).

Salmonella spp. rarely cause PPIs; however, in 98% of detected cases of *Salmonella* spp., the causative agents are *Salmonella enteritidis* and *Salmonella typhi*. *S. typhi* is considered a very rare causative agent of PPIs. Bacteria of this genus can form biofilms. It is more often found in the hip joint than the knee one. It occurs in people with immunodeficiency (Rajgopal *et al.*, 2017).

The Micrococcaceae family

Periprosthetic infections caused by *Falsarthrobacter nasiphocae* (*Arthrobacter nasiphocae*) is often detected as a mixed culture along with *Corynebacterium phocae*, *P. aeruginosa*, and *Staphylococcus aureus*. *F. nasiphocae* is resistant to ceftriaxone but sensitive to vancomycin, co-trimoxazole, doxycycline, penicillin, and ciprofloxacin. In treatment of PPI caused by *F. nasiphocae*, large doses of antibiotics are required, because *F. nasiphocae* is found in biofilms, allowing it to protect itself from the effects of antimicrobial drugs (Tay *et al.*, 2023).

The Clostridiaceae family

Periprosthetic infections caused by pathogens of the Clostridiaceae family are rare (Karczewski *et al.*, 2021). *Clostridium difficile* and *C. perfringens* are most often isolated (Hersh *et al.*, 2019). Laboratory diagnosis of PPIs caused by *Clostridium* spp. is strictly dependent on tissue sampling and treatment. It can be complicated by the fact that *Clostridium* bacterium is more often detected in mixed infections.

Clostridium difficile refers to anaerobic spore-forming Gram-positive bacterium that produces a toxin. This pathogen usually leads to pseudomembranous colitis with manifestations of diarrhea and abdominal pain (Stokey *et al.*, 2023; Deckey *et al.*, 2024). According to literature data, a total of 5 cases of PPIs caused by *C. difficile* have been reported, two of which resulted in amputation. Only 1% of all *C. difficile* infections occurs outside the intestine (Stokey *et al.*, 2023; Deckey *et al.*, 2024).

The Mycobacteriaceae family

Periprosthetic infections caused by pathogens of the

Mycobacteriaceae family occur in 0.6% of reported cases of all PPIs (Dasari *et al.*, 2022; Liu *et al.*, 2024). Non-tuberculous mycobacteria are considered atypical pathogens of PPI and are divided into two categories, mainly fast- and slow-growing. The first group includes *Mycobacterium abscessus*, *M. chelonae*, and *M. fortuitum*, while the slow-growing ones include *M. kansasii* and *M. goodii* (Maimaiti *et al.*, 2023; Damronglerd *et al.*, 2024). *M. abscessus* is a representative of non-tuberculous mycobacteria and includes 3 subspecies: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *bolletii*, and *M. abscessus* subsp. *Massiliense*. *M. abscessus* is capable of colonizing artificial surfaces and medical instruments, and is resistant to disinfectants (Kasimova *et al.*, 2023). *M. abscessus* can affect the skin, soft tissues, bones, joints, lymph nodes, internal organs, and forms characteristic granulomas (Kasimova *et al.*, 2023). Tendon sheaths, joints, and bones can become infected as a result of various injuries, surgical procedures, and/or invasive procedures. With ineffective treatment, relapses and complications may occur, fatal cases were also reported. This pathogen is characterized by high natural resistance to a wide range of antibacterial drugs; therefore, it is necessary to prescribe at least three antibiotics to which *M. abscessus* is sensitive (Genovese *et al.*, 2021; Kasimova *et al.*, 2023). *M. houstonense* is a fast-growing, acid-resistant Gram-positive bacterium that does not form spores. One case of PPI caused by *M. houstonense* has been officially registered (Li *et al.*, 2023). *M. kansasii* is a non-tuberculous mycobacterium that rarely leads to PPIs. It often leads to infections of the respiratory system and skin (Dasari *et al.*, 2022; Maimaiti *et al.*, 2023). The most likely pathway of transmission of this pathogen is through the skin. *M. tuberculosis* causes PPIs with a frequency of 0.3%. It mainly affects large joints (Guan and Zeng, 2021; Dasari *et al.*, 2022). *M. fortuitum* more often affects the knee joint, very rarely the hip one (Ramanathan and Ayoade, 2021).

The Pseudomonadaceae family

Pseudomonas aeruginosa occurs in 8% of cases of all PPI (Leggett *et al.*, 2022; Tsiskarashvili *et al.*, 2022). It is the most frequently isolated pathogen among representatives of Gram-negative bacteria (Hsieh *et al.*, 2009). *P. aeruginosa* is included in the ESKAPE list (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.); a list of the most significant pathogens that account

for most of the morbidity and mortality attributed to multidrug resistance (Kozlov *et al.*, 2024). This microorganism is characterized by wide metabolic adaptability due to its large genome (Moyano *et al.*, 2014). *P. aeruginosa* is one of the bacteria that can form biofilms on the surface of a prosthesis (Neut *et al.*, 2005). The incidence of PII of the knee joint caused by *P. aeruginosa* is 4.4%, while of the hip joint is 3.7% (Barros *et al.*, 2022).

The Moraxellaceae family

Acinetobacter baumannii is a widespread nosocomial pathogen included in the ESKAPE list (Kozlov *et al.*, 2024). It accounts for 7.4% of all bacterial PPI (Tsiskarashvili *et al.*, 2022). This pathogen is capable of forming biofilms on the surface of prosthesis (Neut *et al.*, 2005). Mortality rate in the presence of this pathogen is about 30% (Canty *et al.*, 2017). PPI caused by multi-drug resistant *A. baumannii* is one of the most difficult complications in orthopedic practice detected in the European population, with multidrug resistance observed in 36.8% of *Acinetobacter* strains.

The Propionibacteriaceae family

According to literature data, *Propionibacterium granulosum* rarely leads to PPI (Nikolaev *et al.*, 2021). In PPI associated with *Cutibacterium acnes*, inflammatory markers are higher if the infectious process is localized in the knee and hip joint, compared to the shoulder joint. However, other studies have reported the opposite. *Propionibacterium* is a pathogen that is often found in infected arthroplasty of the shoulder, less often in infections of the knee or hip joint (Vasiliadis *et al.*, 2021). *Propionibacterium acnes* is the most common cause of PPI of the shoulder joint because it is found mainly in the dermal and epidermal layers of the shoulder as a result of a large number of hair follicles and sebaceous glands (Paxton *et al.*, 2019; Sewpaul *et al.*, 2022; Nelson *et al.*, 2023). In turn, *Cutibacterium avidum* more often leads to hip inflammation (Egglestone *et al.*, 2019).

Periprosthetic infections caused by fungi

Fungal infections are atypical because they occur very rarely, representing 1-2% of all infections (Chisari *et al.*, 2022; Fusini *et al.*, 2023). The prognosis for fungal infections is not always favorable, since some fungal strains are resistant to modern drugs, leading to arthrodesis, lifelong spacer insertion, and/or even amputation (Azad *et al.*, 2022; Fusini *et al.*, 2023; Lin *et al.*, 2022). In case of fungal infections, the prosthesis

must necessarily be removed, because of high risk of infection recurrence (Tabliago *et al.*, 2022).

It is believed that PPIs of fungal etiology are more common in people with a reduced immune response, resulting from malignant neoplasms, use of antitumor agents; corticosteroids, immunosuppressants, uncontrolled and improper use of antibiotics, in addition to tuberculosis, diabetes, use of narcotic substances, and acquired immunosuppressive diseases (Escolà-Vergé *et al.*, 2021). Due to biofilm formation, fungi are capable of persistence and have antimicrobial resistance, leading to a greater risk of chronization and recurrence of infection, in contrast to bacterial aetiology (Lin *et al.*, 2022; Fusini *et al.*, 2023).

Fungal infections are most often induced by fungi of the genus *Candida*, causing approximately 80% of all fungal infections (Rienmüller and Borens, 2016; Dobrovol'skaya *et al.*, 2020; Azad *et al.*, 2022; Chisari *et al.*, 2022). The most common species of these are *C. albicans* (55-65%) and *C. parapsilosis* (13-33%) (Bozhkova *et al.*, 2019; Escolà-Vergé *et al.*, 2021; Menotti *et al.*, 2024). *Cryptococcus neoformans*, *Pseudallescheria boydii*, *Candida lipolytica*, *Candida lusitanae*, *Alternaria infectoria*, *Rhodotorula minuta*, *Aspergillus* spp., *Pithomyces* spp., *Aureobasidium* spp., *Hormonema* spp. and *Coccidioides* spp. occur in 1-2% only of cases. However, in 15-20% of cases, PPIs caused by fungi occur with concomitant bacterial infections (Vasoo *et al.*, 2014; Fusini *et al.*, 2023). According to the major European and American reference centers, occurrence of a particular fungal species depends on geographical location. Thus, in Southeast Asia, the most common pathogens are *C. albicans* and *C. parapsilosis* (Vasoo *et al.*, 2014). Unlike other species, *C. albicans* forms a larger and more complex biofilms (Menotti *et al.*, 2024).

Acremonium spp. are very rare, they affect various organs and systems such as the eyes, lungs, and gastrointestinal tract. In a recent study, it was proved that *Acremonium kiliense* and *Acremonium egyptiacum* are involved in the occurrence of PPIs. They are sensitive to voriconazole (Chisari *et al.*, 2022). Fungi of the genus *Aspergillus*, *Aureobasidium*, *Talaromyces*, *Cryptococcus*, *Malassezia*, and others are less common.

The clinical symptoms of fungal PPI are mild and not acute, which distinguish them from bacterial PPI. When treating PPI caused by fungi, a two-

stage surgical intervention and a systemic antifungal therapy are effective. The first stage involves inserting a spacer with amphotericin B, and the second stage involves revision joint replacement (Escolà-Vergé *et al.*, 2021; Fusini *et al.*, 2023).

Periprosthetic infections of polymicrobial etiology

Polymicrobial infections are reported in about 15% of PPI cases, and no recommendations are accepted for management of such patients (Flurin *et al.*, 2019). In case of mixed bacterial and fungal infections, combinations of sanitation and antimicrobial drugs are necessary for successful treatment of such infections. Specifically, patients with diabetes have an increased risk of polymicrobial infections (Ergin *et al.*, 2024).

Conclusions and Recommendations

In the treatment and diagnosis of PPIs, it is necessary to take into account the complex relationships of micro- and macroorganisms, and the influence of the prosthesis. To reduce the likelihood of PPIs, careful preoperative preparation should be carried out, including treatment of foci of chronic infections, decolonization of *Staphylococcus aureus* in carriers, and compliance with aseptic and antiseptic rules. When creating orthopedic devices, it is necessary to create coatings that prevent the development of microorganisms and biofilms, while simultaneously capable of rapid bio-integration with host tissues. Studying the microbiological spectrum of the main causative agents of PPIs will allow us to create more accurate and faster laboratory tests, rationally approaching antibacterial therapy, and narrowing the range of used antibiotics.

Due to the fact that PPIs may be caused by wide range of various microorganisms, it is recommended to use modern high-tech laboratory diagnostic methods, including Matrix-activated laser desorption/ionization, time-of-flight mass spectrometry, and NGS methods for rapid and correct diagnosis. The use of these modern methods certainly contributes to making a more accurate and timely diagnosis and prescribing optimal therapy, which will reduce the complications and economic damages caused by PPIs.

Acknowledgement

The authors are very grateful to the rector, as well as Vice-Rector of research and innovation of Samara

State Medical University for their support.

Novelty Statement

The novelty of this review is that it presents current data on pathogens that cause periprosthetic joint infection. It describes the main groups of microorganisms, including rare and atypical pathogens, which are identified using modern laboratory diagnostic methods, such as MALDI-ToF mass spectrometry and sequencing.

Author's Contribution

Andrei Vladimirovich Kozlov: Conceptualization, data curation, supervision, writing review and editing, project administration.

Artem Viktorovich Lyamin: Conceptualization, writing review and editing, project administration.

Araik Levikovich Misakyan and Aleksei Alekseevich Neilenko: Conceptualization, writing original draft, writing review editing.

Dmitry Sergeevich Kudashev: Conceptualization, writing review editing.

Maria Yur'yevna Sefedinova: Writing review editing.

Ethical approval

Non-applicable.

Funding source

This work was not funded by any source.

Generative AI and AI-assisted technology statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Conflict of interests

The authors have declared no conflicts of interest.

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