



Systematic Review of Bacterial Pathogens Associated with Prosthetic Joint Infection after Total Knee Arthroplasty

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Article info

Received: 28.03.2026

Accepted: 10.06.2026

Available Online: 23.06.2026

Checked for Plagiarism: Yes

Keywords:

Mediterraneibacter gnavus;
prosthetic joint infection;
anaerobic bacteria; MALDI-TOF
mass spectrometry

ABSTRACT

Introduction: Prosthetic joint infection (PJI) remains one of the most serious complications following total knee arthroplasty, leading to substantial morbidity, repeated surgical procedures, and increased healthcare burden. These infections are primarily driven by bacterial colonization and biofilm formation on implant surfaces. Given the variability in reported causative microorganisms, the aim of this study was to systematically review the literature to identify the bacterial pathogens most commonly associated with PJI after total knee arthroplasty.

Material and methods: This systematic review followed PRISMA guidelines to identify bacterial pathogens associated with prosthetic joint infection after total knee arthroplasty. Studies were retrieved from PubMed, Web of Science, ScienceDirect, and Google Scholar using structured keywords. Two reviewers independently screened articles, and methodological quality of eligible observational studies was assessed using the Joanna Briggs Institute appraisal tools.

Results: Across four published case reports (n=4), Ruminococcus/Mediterraneibacter gnavus was implicated in prosthetic joint infection (25%), deep surgical site infection (25%), bacteraemia (25%), and septic arthritis (25%), predominantly in elderly or immunocompromised patients. Identification relied on MALDI-TOF and/or 16S rRNA sequencing in all cases (100%), and favorable clinical outcomes were achieved with combined surgical management and targeted antibiotic therapy in the majority of reported infections.

Conclusion: Mediterraneibacter gnavus should be recognized as a rare but clinically significant opportunistic pathogen capable of causing orthopedic and systemic infections. Accurate diagnosis depends on advanced microbiological techniques, and outcomes appear favorable with timely surgical intervention and targeted antimicrobial therapy. Increased awareness may facilitate earlier detection and appropriate management.

Introduction

Total knee arthroplasty (TKA) is widely recognized as one of the most successful surgical interventions for the management of advanced knee osteoarthritis and other debilitating joint diseases. With the aging global population and the increasing prevalence of degenerative joint disorders, the number of TKA procedures performed worldwide has risen steadily

over the past decades. This procedure significantly improves pain, mobility, and quality of life for millions of patients. Despite these favorable outcomes, prosthetic joint infection (PJI) remains one of the most serious and challenging complications following TKA. Although the incidence of infection relatively low compared with the total number of procedures performed, the

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clinical consequences can be devastating for patients and healthcare systems. PJI is associated with prolonged hospitalization, repeated surgical procedures, increased healthcare costs, and substantial morbidity. Therefore, understanding the microbial causes of these infections is essential for improving prevention, diagnosis, and treatment strategies (1).

Prosthetic joint infection is a complex condition that results from microbial colonization of the prosthetic surface and surrounding tissues. Once bacteria adhere to the implant surface, they can form biofilms structured communities of microorganisms embedded in a protective extracellular matrix. Biofilm formation significantly complicates the treatment of PJI because bacteria within biofilms exhibit increased resistance to host immune responses and antimicrobial agents. This biological phenomenon allows pathogens to persist in the per prosthetic environment even in the presence of aggressive antibiotic therapy. Consequently, infections associated with biofilms often require combined surgical and medical management, including debridement, implant retention or removal, and prolonged antibiotic therapy. Understanding which bacterial species are most commonly involved in these infections is therefore fundamental to optimizing therapeutic decision-making and improving patient outcomes (2).

Among the pathogens implicated in prosthetic joint infections, Gram-positive bacteria are consistently reported as the most frequent causative organisms. *Staphylococcus aureus* and coagulase-negative staphylococci, particularly *Staphylococcus epidermidis*, are commonly isolated from infected prosthetic joints. These microorganisms possess specific virulence factors that facilitate adherence to biomaterial surfaces and promote biofilm formation. In addition to staphylococcal species, other Gram-positive organisms such as streptococci and enterococci have also identified in a proportion of PJI cases. The predominance of these organisms highlights the importance of skin flora as a major source of contamination during or after surgical implantation. Preventive strategies, including perioperative antibiotic prophylaxis, strict aseptic surgical techniques, and optimized operating room environments, are therefore critical for minimizing the risk of bacterial contamination during TKA procedures (3).

Although Gram-positive organisms dominate the microbial spectrum of prosthetic joint infections, Gram-negative bacteria increasingly recognized as significant contributors in certain patient populations. Pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* species, and *Enterobacter* species have reported in various clinical studies. Gram-negative PJIs are often associated with complicated clinical courses and may present challenges in antimicrobial selection

due to intrinsic or acquired resistance mechanisms. These infections are frequently observed in patients with comorbid conditions, immunosuppression, or prolonged hospitalization. In addition, polymicrobial infections involving both Gram-positive and Gram-negative organisms may occur, further complicating clinical management and therapeutic decision-making. The presence of multidrug-resistant organisms in some cases underscores the growing concern regarding antimicrobial resistance in orthopedic infections (4). Several factors contribute to the development of prosthetic joint infection following total knee arthroplasty. These include patient-related factors such as advanced age, obesity, diabetes mellitus, rheumatoid arthritis, malnutrition, and immune compromise. Surgical factors also play a crucial role, including operative duration, surgical technique, perioperative contamination, and postoperative wound complications. Environmental factors within the operating room, including airflow systems and sterility protocols, may influence the risk of microbial exposure. Moreover, postoperative bacteremia originating from remote infections can seed the prosthetic joint and lead to late infections. The interaction between host susceptibility, microbial virulence, and implant characteristics ultimately determines the likelihood of infection development and progression (5).

The timing of prosthetic joint infection after TKA is often categorized into early, delayed, and late infections, each associated with distinct microbial profiles and clinical features. Early infections typically occur within the first few weeks after surgery and frequently caused by highly virulent organisms such as *Staphylococcus aureus*. Delayed infections, which develop months after implantation, are commonly associated with less virulent organisms such as coagulase-negative staphylococci that form biofilms and produce subtle clinical manifestations. Late infections may occur years after the procedure and are often the result of hematogenous spread from distant infection sites. Understanding the temporal patterns of infection can help clinicians anticipate the likely causative organisms and guide empirical antibiotic therapy while awaiting microbiological confirmation (6).

Accurate identification of the bacterial pathogens responsible for prosthetic joint infection is essential for selecting appropriate antimicrobial therapy and determining the optimal surgical strategy. Traditional diagnostic methods include microbiological culture of synovial fluid, per prosthetic tissue samples, removed prosthetic components. However, culture-negative infections remain a clinical challenge and may occur due to prior antibiotic exposure or the presence of slow-growing microorganisms embedded within biofilms. In recent years, advanced molecular diagnostic techniques, including polymerase chain

reaction (PCR) assays and next-generation sequencing, have explored as complementary approaches to improve pathogen detection. These technologies have the potential to identify previously unrecognized microorganisms and provide deeper insights into the microbiological landscape of prosthetic joint infections (7).

Given the clinical complexity and significant burden associated with PJI after total knee arthroplasty, numerous studies have investigated the microbiological patterns of infection in different geographic regions and healthcare settings. However, the reported prevalence of specific bacterial pathogens varies considerably across studies. Differences in study design, patient populations, diagnostic criteria, and laboratory methods may contribute to this variability. Furthermore, evolving antimicrobial resistance patterns and changes in surgical practices may influence the distribution of causative organisms over time. As a result, synthesizing evidence from multiple studies is necessary to provide a clearer and more comprehensive understanding of the bacterial spectrum associated with PJI following TKA (8).

Systematic reviews play a critical role in summarizing available evidence and identifying trends within the existing literature. By applying structured search strategies, predefined inclusion criteria, and standardized methods for data extraction and analysis, systematic reviews reduce bias and enhance the reliability of synthesized findings. In the context of prosthetic joint infections, a systematic evaluation of bacterial pathogens can provide valuable insights into the most frequently encountered organisms and their relative prevalence. Such information is particularly important for guiding empirical antibiotic therapy, improving infection prevention strategies, and informing clinical decision-making in orthopedic practice (9).

In addition, understanding the microbiological characteristics of prosthetic joint infections has important implications for public health and healthcare resource allocation. PJIs are associated with significant economic costs due to extended hospitalization, revision surgeries, long-term antibiotic therapy, and rehabilitation requirements. Early identification of common pathogens and their resistance patterns may facilitate the development of targeted preventive measures and antimicrobial stewardship programs. These strategies are essential for minimizing infection rates, optimizing patient outcomes, and reducing the overall burden of orthopedic infections on healthcare systems worldwide (10).

Given the growing number of total knee arthroplasty procedures performed globally and the serious consequences of prosthetic joint infections, it is essential to consolidate existing evidence regarding the bacterial pathogens responsible for these

infections. A comprehensive synthesis of the literature can help clarify the distribution of causative organisms and identify patterns that may inform future research and clinical practice. Therefore, the aim of the present study is to review published evidence on bacterial pathogens associated with prosthetic joint infection following total knee arthroplasty. This study conducted as a systematic review to critically evaluate and summarize the available data on the microbiological profile of these infections and to provide a clearer understanding of the organisms most frequently implicated in this serious postoperative complication.

Material and methods

Study Design

This study conducted as a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review aimed to identify and synthesize published evidence regarding bacterial pathogens associated with prosthetic joint infection following total knee arthroplasty through a structured and transparent methodology for study identification, selection, and data synthesis.

Eligibility Criteria

Studies were considered eligible if they met the following inclusion criteria: original research articles reporting bacterial pathogens associated with prosthetic joint infection after total knee arthroplasty; studies involving human subjects; observational study designs including cohort studies, case-control studies, cross-sectional studies, and case series with clearly reported microbiological findings; studies that provided identifiable data on bacterial isolates from infected prosthetic knee joints; and articles published in English. In addition, studies were required to present sufficient methodological information and microbiological results to allow extraction of pathogen-related data. The exclusion criteria included review articles, systematic reviews, meta-analyses, editorials, conference abstracts without full text, letters to the editor, animal studies, *in vitro* studies, duplicate publications, and studies that did not specifically report bacterial pathogens related to prosthetic joint infection following total knee arthroplasty. Studies focusing exclusively on hip arthroplasty infections, studies lacking clear microbiological identification of pathogens, and articles with insufficient or incomplete data also excluded from the review.

Databases and Information Sources

A comprehensive literature search performed across several electronic databases, including PubMed/MEDLINE, Web of Science, Science Direct, and Google Scholar, to identify relevant studies published on bacterial pathogens associated

with prosthetic joint infection following total knee arthroplasty.

Search Keywords

The search strategy incorporated a wide range of keywords and Medical Subject Headings (MeSH) related to prosthetic joint infection and bacterial pathogens. The primary search terms included combinations of “prosthetic joint infection,” “per prosthetic joint infection,” “PJI,” “total knee arthroplasty,” “total knee replacement,” “knee prosthesis infection,” “bacterial pathogens,” “bacteria,” “microbial pathogens,” “microbiology,” “infectious agents,” “Staphylococcus aureus,” “coagulase-negative staphylococci,” “Staphylococcus epidermidis,” “Streptococcus,” “Enterococcus,” “Gram-positive bacteria,” “Gram-negative bacteria,” “Pseudomonas

aeruginosa,” “Escherichia coli,” and “Klebsiella.” These terms were combined using Boolean operators such as and OR to maximize the sensitivity and comprehensiveness of the search process.

Search Strategy

The literature search and study selection process were performed independently by two reviewers to minimize selection bias. Titles and abstracts were initially screened, followed by full-text assessment of potentially eligible articles. Any disagreements between the reviewers were resolved through discussion and consensus. The detailed search strategy applied in the PubMed database is presented in Table 1.

Table 1. PubMed Search Strategy for Identifying Relevant Studies

Search Number	Search Query
#1	“Prosthetic Joint Infection” OR “Per prosthetic Joint Infection” OR PJI
#2	“Total Knee Arthroplasty” OR “Total Knee Replacement” OR “Knee Prosthesis”
#3	“Bacterial Pathogens” OR Bacteria OR “Microbial Pathogens” OR Microbiology
#4	“Staphylococcus aureus” OR “Staphylococcus epidermidis” OR “Coagulase-negative Staphylococci”
#5	“Gram-positive bacteria” OR “Gram-negative bacteria” OR “Pseudomonas aeruginosa” OR “Escherichia coli” OR “Klebsiella”
#6	#1 AND #2 AND (#3 OR #4 OR #5)

Quality Assessment of Included Studies

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools appropriate for observational studies. This instrument evaluates several methodological domains, including selection bias, measurement of exposure and outcomes, confounding factors, and completeness of data reporting. Each study was independently evaluated by two reviewers to determine the overall risk of bias and methodological reliability of the included evidence.

Institute (JBI) critical appraisal checklist for case reports. Overall, the studies demonstrated generally acceptable methodological quality, with most domains adequately reported. Key elements such as clear patient description, diagnostic methods, intervention details, and clinical outcomes were consistently documented. However, minor limitations were observed in some reports regarding comprehensive patient history or follow-up details (figure 2).

Results

A total of 750 records were identified through database searching, with no additional records retrieved from other sources. After duplicate removal, 750 records remained for screening, of which 525 were screened and 385 were excluded. Subsequently, 140 full-text articles were assessed for eligibility, and 4 studies were ultimately included in the qualitative synthesis (figure 1).

The methodological quality of the four included case reports was evaluated using the Joanna Briggs

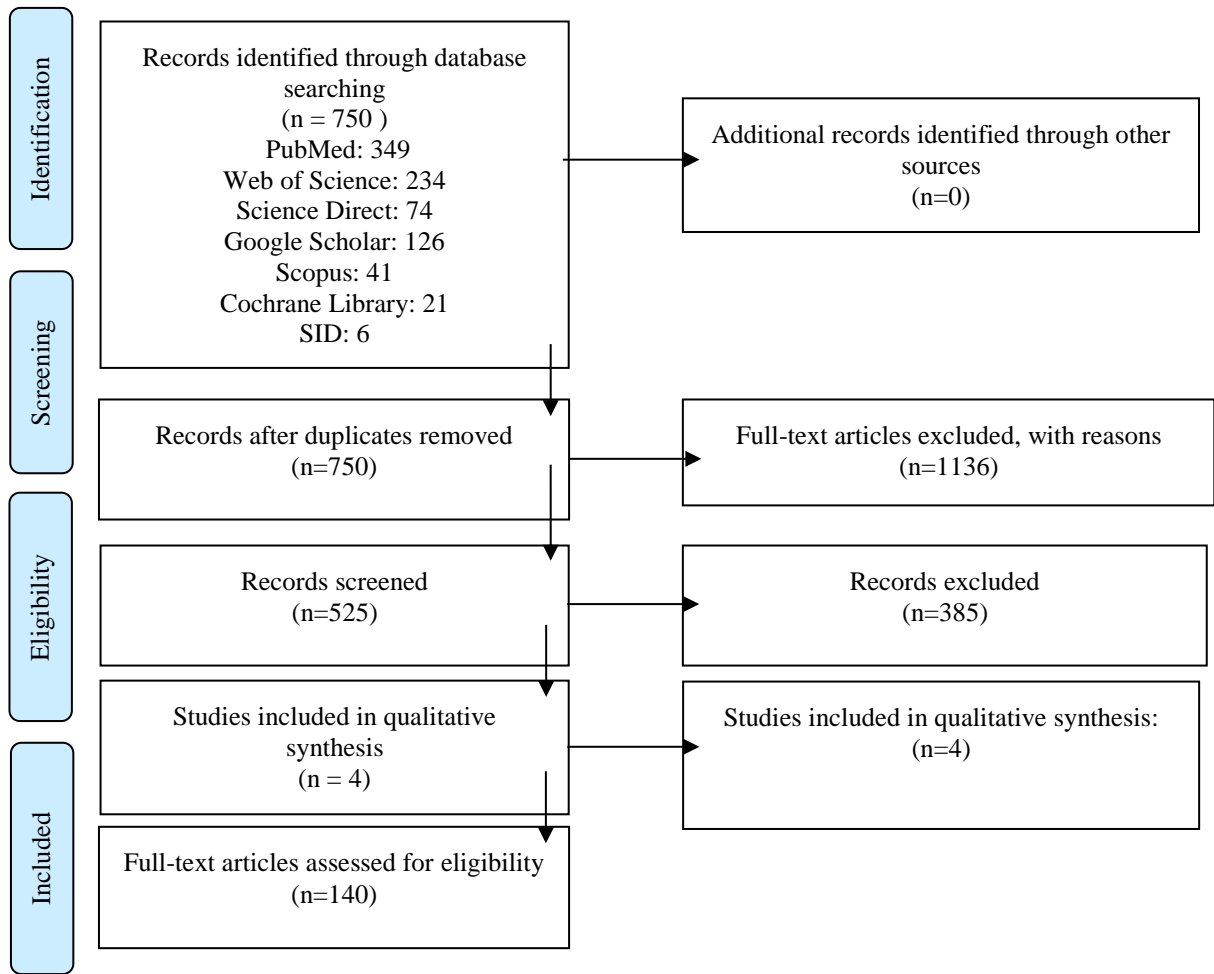


Figure 1. PRISMA guanidine

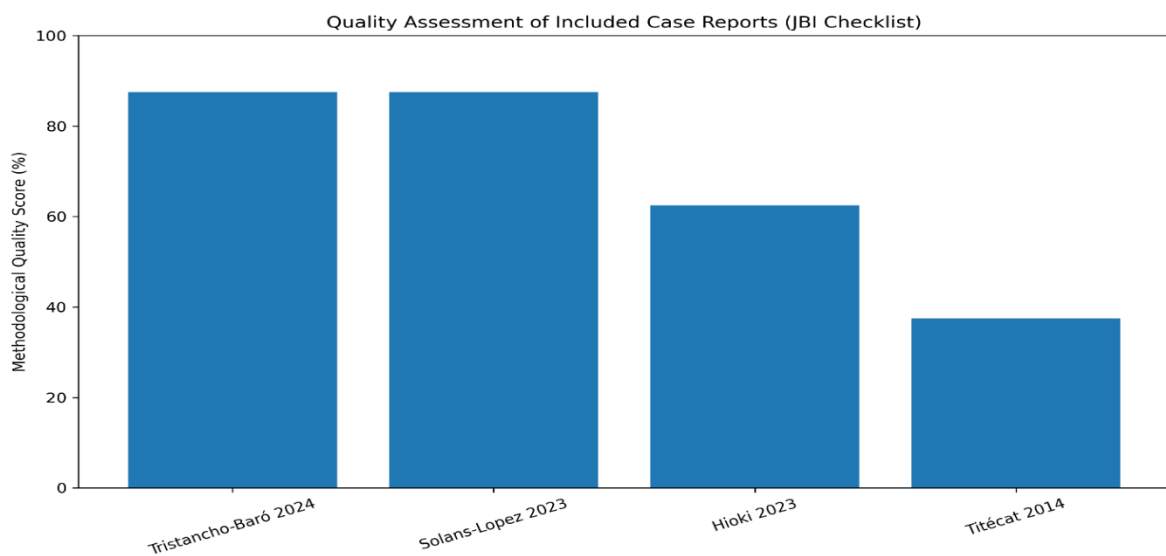


Figure 2. Quality Assessment of Included Case Reports

The reviewed case reports highlight the rare but clinically relevant role of *Ruminococcus gnavus* (currently classified as *Mediterraneibacter gnavus*) in orthopedic and systemic infections. Tristancho-Baró et al. (2024) described a prosthetic joint infection occurring 20 days after total knee arthroplasty in a 74-year-old patient, in which the organism was identified through anaerobic culture, MALDI-TOF mass spectrometry, and confirmed by 16S rRNA sequencing; the patient was successfully treated with debridement, antibiotics, implant retention, and prolonged oral amoxicillin therapy. Similarly, Solans-Lopez et al. (2023) reported a deep surgical site infection after posterior spinal instrumentation in an 81-year-old woman, where multiple anaerobic cultures confirmed *R. gnavus* using MALDI-TOF, and the infection resolved following surgical debridement and antibiotic therapy with amoxicillin and ciprofloxacin. In another report, Hioki et al. (2023) documented *R.*

gnavus bacteremia in a 73-year-old immunocompromised patient with sigmoid colon perforation, highlighting notable morphological variability of the organism on Gram staining, which may complicate early laboratory recognition. Earlier evidence from Titécat et al. (2014) described septic arthritis caused by *R. gnavus*, with identification achieved through mass spectrometry and confirmation by 16S rRNA sequencing. Collectively, these reports demonstrate that although *R. gnavus* is primarily a commensal organism of the human gastrointestinal tract, it can occasionally act as an opportunistic pathogen in musculoskeletal and systemic infections. Accurate diagnosis in these cases often relies on advanced microbiological techniques, including MALDI-TOF and molecular sequencing, which facilitate reliable identification of this uncommon anaerobic pathogen (table 2).

Table 2. Summary of Reported Infections Caused by *Ruminococcus/Mediterraneibacter gnavus*

Study	Study Design	Patient Characteristics	Infection Type	Pathogen	Diagnostic Method	Treatment	Key Findings
Tristancho-Baró et al., 2024 (11)	Case report	74-year-old patient; symptoms 20 days after total knee arthroplasty	Prosthetic joint infection (PJI)	<i>Mediterraneibacter gnavus</i> (formerly <i>Ruminococcus gnavus</i>), Gram-positive anaerobic diplococcus	Anaerobic synovial fluid culture; MALDI-TOF; confirmed by 16S rRNA sequencing	DAIR + vacuum-assisted therapy; oral amoxicillin for 3 months	Rare anaerobic cause of PJI; highlights importance of advanced diagnostic identification
Solans-Lopez et al., 2023 (12)	Case report	81-year-old woman after posterior spinal instrumentation	Deep surgical site infection (SSI)	<i>Ruminococcus gnavus</i> , anaerobic Gram-positive coccus	Six anaerobic cultures positive; identification by MALDI-TOF mass spectrometry	Surgical irrigation and debridement; amoxicillin + ciprofloxacin for 4 weeks	Suggests intestinal disease or immunosuppression as potential risk factors
Hioki et al., 2023 (13)	Case report	73-year-old immunocompromised man with sigmoid colon perforation	Bacteraemia	<i>Ruminococcus gnavus</i> , Gram-positive anaerobic coccus	Blood culture; Gram staining; anaerobic subculture	Not specified in summary	Demonstrated morphological diversity on Gram stain which may complicate preliminary laboratory identification
Titécat et al., 2014 (14)	Case report	Adult patient (details not specified in summary)	Septic arthritis	<i>Ruminococcus gnavus</i> , anaerobic Gram-positive coccus	Identification by mass spectrometry; confirmation with 16S rRNA sequencing	Not specified in summary	Demonstrates that <i>R. gnavus</i> can rarely cause septic arthritis and requires molecular methods for accurate identification

Discussion

The present findings collectively demonstrate that *Ruminococcus gnavus*, currently reclassified as *Mediterraneibacter gnavus*, although predominantly recognized as a commensal anaerobic bacterium of the human gastrointestinal tract, can act as an opportunistic pathogen in musculoskeletal and systemic infections. The reviewed cases illustrate its

involvement in prosthetic joint infection, deep surgical site infection following spinal instrumentation, bacteremia in the context of gastrointestinal perforation, and septic arthritis. Across these reports, advanced microbiological techniques particularly MALDI-TOF mass spectrometry and 16S rRNA gene sequencing were essential for accurate identification. Clinical

outcomes were generally favorable when prompt surgical management and targeted antimicrobial therapy were implemented, underscoring both the pathogenic potential of this organism and the importance of precise laboratory diagnosis.

The emergence of *M. gnavus* as a clinically relevant pathogen in orthopedic and invasive infections may be explained by its ecological niche within the gastrointestinal microbiota and its potential for translocation under conditions of mucosal barrier disruption or systemic vulnerability. This organism is a common constituent of the intestinal microbiome and has been associated with inflammatory bowel conditions and altered gut permeability. Surgical stress, advanced age, malignancy, immunosuppression, or instrumentation procedures may facilitate bacterial translocation from the gut into the bloodstream or adjacent tissues. Once systemic dissemination occurs, hematogenous seeding of prosthetic material or damaged tissue may ensue. The reviewed cases, particularly those involving elderly or immunocompromised patients, support this pathophysiological mechanism and highlight host susceptibility as a key determinant in opportunistic infection development (15).

Another important consideration is the increasing use of implanted medical devices, such as prosthetic joints and spinal instrumentation, which create surfaces susceptible to microbial adherence and biofilm formation. Although biofilm production by *M. gnavus* has not been as extensively characterized as that of classical orthopedic pathogens such as *Staphylococcus aureus*, anaerobic Gram-positive cocci are known to possess adhesion mechanisms that enable colonization of prosthetic material. The prosthetic joint infection described shortly after arthroplasty suggests either perioperative contamination or early hematogenous spread. The successful management with debridement, antibiotics, and implant retention implies that early detection and intervention can overcome biofilm-associated persistence, particularly when the organism demonstrates susceptibility to beta-lactam antibiotics (16).

The diagnostic challenges observed in these cases further explain why infections due to *M. gnavus* are rarely reported. Conventional culture techniques may underestimate anaerobic pathogens, especially when specimens are not handled under strict anaerobic conditions or when incubation periods are insufficient. Additionally, morphological variability on Gram staining, as described in the case of bacteremia, may delay or obscure recognition. Such pleomorphic can lead to misclassification as other Gram-positive cocci or even contamination. The widespread adoption of MALDI-TOF mass spectrometry in clinical microbiology laboratories has significantly improved the identification of fastidious and uncommon organisms, including

anaerobes that were previously difficult to characterize. Confirmation with 16S rRNA sequencing further enhances diagnostic precision, particularly in rare infections where phenotypic databases may be limited (17).

The therapeutic responses described in the reviewed reports are consistent with the known antimicrobial susceptibility profile of *M. gnavus*. This species is generally susceptible to beta-lactams, including penicillin and amoxicillin, although resistance patterns may vary depending on local microbiota dynamics and prior antibiotic exposure. The favorable outcomes following amoxicillin-based regimens support the continued role of targeted therapy guided by susceptibility testing. In orthopedic infections, combined surgical and antimicrobial strategies remain the cornerstone of management. The resolution of infection after debridement and prolonged oral therapy suggests that early-stage infections caused by anaerobic commensals may respond well when addressed promptly. However, the absence of standardized treatment guidelines for such rare pathogens underscores the need for individualized management plans based on clinical severity and microbiological data (19).

The gastrointestinal origin hypothesis is particularly compelling in cases associated with intestinal pathology or perforation. Disruption of mucosal integrity permits translocation of commensal bacteria into the bloodstream, leading to bacteremia and potential metastatic infection. In immunocompromised hosts, impaired immune surveillance further increases susceptibility to systemic spread. The association between *M. gnavus* and inflammatory bowel disease described in microbiome research suggests that alterations in gut microbial composition and local inflammation may facilitate pathogenic behavior. Therefore, detection of this organism in sterile sites should prompt clinicians to consider underlying gastrointestinal conditions or mucosal compromise as potential sources (19).

An additional explanation for the increasing recognition of *M. gnavus* infections lies in advancements in microbiome science and taxonomic reclassification. The transition from *Ruminococcus gnavus* to *Mediterraneibacter gnavus* reflects ongoing refinement in bacterial phylogeny based on genomic sequencing. Such reclassification may contribute to underreporting or confusion in earlier literature, as historical cases might not have been accurately categorized. As molecular diagnostics become more accessible, clinicians and microbiologists are better equipped to detect rare anaerobes, which may reveal that these infections are not necessarily novel but previously underdiagnosed (20).

Despite these insights, the rarity of reported cases limits definitive conclusions regarding incidence,

virulence factors, and optimal management strategies. Most available evidence derives from isolated case reports without long-term follow-up or comparative analysis. Consequently, the true pathogenic potential of *M. gnavus* remains incompletely defined. It is unclear whether specific strains possess enhanced virulence determinants, such as polysaccharide capsules, toxin production, or biofilm-forming capacity, that predispose to invasive disease. Future genomic and proteomic investigations could clarify strain-level differences and identify markers associated with clinical severity (21).

From a clinical perspective, these findings emphasize the importance of considering anaerobic organisms in postoperative or device-related infections, particularly when routine cultures are negative and inflammatory markers remain elevated. Close collaboration between orthopedic surgeons, infectious disease specialists, and microbiology laboratories is essential to ensure appropriate specimen collection and extended anaerobic incubation. Awareness of this pathogen may reduce diagnostic delay and facilitate early initiation of targeted therapy, thereby improving patient outcomes. In summary, the reviewed evidence demonstrates that *Mediterraneibacter gnavus*, though typically a benign intestinal commensal, can behave as an opportunistic pathogen in orthopedic and systemic infections under conditions of host vulnerability, mucosal disruption, or foreign body implantation. Its detection relies heavily on advanced diagnostic modalities, and clinical outcomes are generally favorable with combined surgical and antimicrobial management. Continued reporting of similar cases and incorporation of molecular diagnostic tools into routine practice will enhance understanding of this uncommon but clinically significant anaerobic bacterium and clarify its evolving role in invasive infections (22).

Conclusion

Although traditionally regarded as a commensal gastrointestinal anaerobe, *Mediterraneibacter gnavus* demonstrates the capacity to cause invasive musculoskeletal and systemic infections, particularly in vulnerable hosts. The reviewed cases underscore the importance of considering anaerobic pathogens in postoperative and device-related infections, especially when conventional cultures are inconclusive. Reliable identification frequently requires MALDI-TOF mass spectrometry and molecular sequencing, reflecting the organism's diagnostic complexity. Clinical outcomes are generally positive when prompt surgical debridement and tailored antibiotic therapy are instituted. Continued reporting and molecular characterization of such cases will improve

understanding of its pathogenic potential and inform future management strategies.

Acknowledgments

All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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