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► To cite this version:

Umile Giuseppe Longo, Alberto Lalli, Benedetta Bandini, Silvia Angeletti, Sebastien Lustig, et al.. The influence of gut microbiome on periprosthetic joint infections: State-of-the art. Journal of ISAKOS, 2024, 10.1016/j.jisako.2024.01.011 . hal-04475297

HAL Id: hal-04475297

<https://univ-lyon1.hal.science/hal-04475297>

Submitted on 23 Feb 2024

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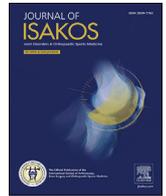
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Journal of ISAKOS

journal homepage: www.elsevier.com/locate/jisakos

State of the Art Review

The influence of gut microbiome on periprosthetic joint infections: State-of-the art

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ARTICLE INFO

Keywords:

PJI
Microbiome
Periprosthetic joint infections
Knee joint replacement

ABSTRACT

Early periprosthetic joint infection constitutes one of the most frightening complications of joint replacement. Recently, some evidence has highlighted the potential link between dysregulation of the gut microbiota and degenerative diseases of joints. It has been hypothesized that microbiome dysbiosis may increase the risk of periprosthetic joint infection by facilitating bacterial translocation from these sites to the bloodstream or by impairing local or systemic immune responses. Although the processes tying the gut microbiome to infection susceptibility are still unknown, new research suggests that the presurgical gut microbiota—a previously unconsidered component—may influence the patient's ability to resist infection. Exploring the potential impact of the microbiome on periprosthetic joint infections may therefore bring new insights into the pathogenesis and therapy of these disorders. For a successful therapy, a proper surgical procedure in conjunction with an anti-bacterial concept is essential. As per the surgical approach, different treatment strategies include surgical irrigation, debridement, antibiotic therapy, and implant retention with or without polyethylene exchange. Other alternatives could be one-stage or two-stage revisions surgery. Interventions that either directly target gut microbes as well as interventions that modify the composition and/or function of the commensal microbes represent an innovative and potentially successful field to be explored. In recent times, innovative therapeutic methods have arisen in the realm of microbiome restoration and the management of gut-related ailments. These progressive approaches offer fresh perspectives on tackling intricate microbial imbalances in the gastrointestinal tract. These emerging therapies signify a shift towards more precise and individualized approaches to microbiome restoration and the management of gut-related disorders. Once a more advanced knowledge of the pathways linking the gut microbiota to musculoskeletal tissues is gained, relevant microbiome-based therapies can be developed. If dysbiosis is proven to be a significant contributor, developing treatments for dysbiosis may represent a new frontier in the prevention of periprosthetic joint infections.

INTRODUCTION

Early periprosthetic joint infection (PJI) constitutes one of the most frightening complications of joint replacement [1,2], frequently related to multiple revision operations, late aseptic loosening, extensive antibiotic therapy, a longer hospital stay, recurrent infections, and a poor functional result [3–6].

Recently, some evidence has highlighted the potential link between dysregulation of the gut microbiota and degenerative diseases of joints [7–9].

The human microbiome is a complex organism made up of the microbial species that live in the human body as well as their molecular products [10]. The microbiome can influence host health and disease by modulating immune responses, metabolic pathways, hormone levels and

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<https://doi.org/10.1016/j.jisako.2024.01.011>

Received 26 May 2023; Received in revised form 16 January 2024; Accepted 18 January 2024

Available online xxx

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neural signaling [11]. The microbiome is an intricate structure of interconnected microbial species. The microbiota constituents are in a dynamic balance that varies with daily dietary fluctuations. As a result, the microbiome is a dynamic network of interacting bacteria rather than a collection of microbial species [12]. Firmicutes and Bacteroidetes dominate the human microbiota in the gastrointestinal tract, accounting for more than 90% of the overall community [13].

The crosstalk between the gut microbiome and the joint environment has been defined as “gut–joint axis,” and has been increasingly documented in the scientific literature, both in human and animal studies [14]. The “gut–joint” axis has its foundation on the possibility of joint–gut communication. It is widely acknowledged that gut bacteria create a diverse spectrum of chemicals, comprising enzymes, short-chain fatty acids, and metabolites [15]; as a result, proinflammatory chemicals produced by bacteria, such as lipopolysaccharide, enter the systemic circulation via the “leaky gut” and cause systematic inflammation in the joints [16,17]. This has caused a significant economic burden on the world with a strong impact on the patients’ quality of life [15].

Over the last decade, advances in high-throughput sequencing as well as computational techniques have enabled us to gain insight into the composition and functional properties of gut microbiota components, resulting in significant improvements in our understanding of the microbiome’s contribution to physiological processes and development of diseases [18]. Emerging research suggests a significant correlation between dysbiosis and non-gastrointestinal related diseases, involving conditions beyond the gastrointestinal tract [19–23]. For instance, several studies have indicated that orthopedic conditions, such as rheumatoid arthritis and osteoporosis, may contribute to dysbiosis [24,25]. While further research is needed to establish causality and elucidate the precise mechanisms, these findings underscore the potential systemic impact of dysbiosis in non-gastrointestinal related diseases, particularly in the context of orthopedic conditions. Of significant relevance is the link between microbiome and PJI, which is an infrequent but grave complication of total joint arthroplasty. PJI occurs when microorganisms adhere to the implant surface and form biofilms that are resistant to antibiotics and host immune defenses [26]. PJI can cause implant loosening, osteolysis, chronic pain and systemic infection.

It has been hypothesized that microbiome dysbiosis may increase the risk of PJI by facilitating bacterial translocation from these sites to the bloodstream or by impairing local or systemic immune responses [27]. In addition, obesity and diabetes mellitus, which are notably associated with an elevated risk of PJI of the hip and knee, are linked to a microbiota imbalance.

However, mutations in the microbiome have been connected to a variety of musculoskeletal diseases [28]. In fact, the alteration of the gut microbiome has been shown to limit the number and efficacy of macrophages, making the body’s immune system less capable to defend itself against pathogenic microorganisms [29,30]. Although the processes linking the gut microbiome to infection susceptibility are still unknown, new research suggests that the presurgical gut microbiota—a previously neglected component—could play a role in the patient’s ability to fight off infection. Therefore, understanding the potential influence of microbiome on PJI may give novel perspectives into the pathophysiology and treatment of these conditions.

In this state-of-the-art the authors highlight and update the current knowledge regarding the link between gut microbiome and its dysregulation and the development of PJI following joint replacement surgery. Also, the authors report the current diagnostic tools and treatment options and propose the future perspectives for the investigations to come.

BODY

Microbiota in periprosthetic joint infections

Total joint arthroplasty represents an effective treatment for late-stage osteoarthritis or previously failed hemiarthroplasties, and has the

power to extremely enhance the patients’ quality of life postoperatively [31]. However, the success of this intervention can be undermined by the growing incidence of PJI [32]. PJI is the main causative agent of total knee arthroplasty (TKA) failure and the third most common factor for total hip arthroplasty (THA) revision. Given the enormous number of arthroplasties conducted each year—by 2030, THA and TKA cases carried every year in the US are predicted to increase to 1.26 million and 935,000 cases, respectively—PJI occurs in less than 1%–2% of primary total joint replacement cases, but the impact is significant nonetheless [33]. The most common causative agents of PJI are coagulase-negative staphylococci, *Staphylococcus aureus*, streptococci, enterococci and Enterobacterales. Propionibacteria, gram-positive anaerobic bacteria and integral components of the normal human skin microbiota can also act as opportunistic infections and cause PJI [34]. However, culture-negative PJI cases are also frequent, suggesting that other microorganisms may be involved [35]. Polymicrobial PJIs, characterized by the presence of multiple simultaneous organisms infecting a single prosthesis, have been linked to unfavorable outcomes in comparison to monomicrobial and culture-negative periprosthetic joint infections, despite their relatively low occurrence. Patients afflicted with polymicrobial infections exhibited a higher likelihood of necessitating salvage procedures or experiencing periprosthetic joint infection-related mortality [36]. Infections linked with prosthetic joints are most commonly classified as early (developing less than 3 months postoperatively), delayed (3–24 months postoperatively), or late (developing more than 24 months postoperatively) [37]. Additionally, it is possible to consider both the length of time following surgery, as well as on the hypothesized route of infection and divide PJIs into positive intraoperative cultures, early postoperative infections, hematogenous infections, and late chronic infections [38,39]. The updated classifications of PJIs are reported in Table 1.

The persistent threat of PJI raises doubts about the accepted theories on the pathogenesis and avoidance of these infections. There are few theoretical definitions of how disruption of the gut microbial ecosystem can lead to changes in peripheral tissues such as bones and joints. As an outcome of research studies examining host–microbe connections, a number of pathways that determine how the microbiome can contribute to inflammation and joint pathology have been suggested: control of dietary absorption, regulation of the immune system’s activity at the gut endothelium, and relocation of microbes and bacterial molecular products throughout the endothelial barrier and into the systemic circulation [10]. Recent research has shown that endogenous sources of bacteria, such as the gastrointestinal system, can cause acute and persistent surgical site infections more frequently [40]. This is particularly true when

Table 1
Validated outcome measures and classifications.

Schafroth et al. [37]:	Tsukayama et al. [39]:	McPherson et al. [52]:
- Early: <3 months	- Infection type <ul style="list-style-type: none"> o Positive intraoperative cultures o Early postoperative infection o Hematogenous infection o Late chronic infection 	- Infection type <ul style="list-style-type: none"> o Early postoperative infection o Hematogenous infection o Late chronic infection
- Delayed: 4 months to 2 years	- Symptoms from baseline <ul style="list-style-type: none"> o <4 weeks o Asymptomatic o >4 weeks 	- Systemic host <ul style="list-style-type: none"> o No compromise o Compromise o Significant compromise
- Late: > 3 years	- Mechanism <ul style="list-style-type: none"> o Exogenous o Hematogenous o Both 	- Local factor <ul style="list-style-type: none"> o No compromise o Compromise o Significant compromise
	- Etiological agent	
	- Clinical presentation	

there is an imbalanced gut flora, by alteration or change of one's normal microbiota balance, "dysbiosis," or decreased gut permeability [41]. The gut microbiota and permeability have been suggested to play a role in influencing immune response to external pathogens, as has previously been demonstrated in other disciplines, since it is apparent that immune response plays a crucial role in the pathophysiology of any disorders, particularly infections [42]. However, in the existing literature, no definitive cause-and-effect relationship has been established in humans, leaving room for further exploration of the complex interplay between these variables.

Dysbiosis affects host–microbe interactions, particularly the microbial impulses given to immune cell populations in the gut lining, and is linked to long-term health issues like obesity, diabetes, and inflammatory bowel disease that linked to the development of PJI [43,44]. Diabetes, obesity, malnutrition, and smoking have all been found as key risk factors for PJI, as have significant variations in the composition of the gut microbiota when compared to healthy individuals [10]. Additionally, modifications to the components of the gut microbiome may lower the number and potency of host macrophages as well as their capacity to respond to a systemic bacterial challenge by modifying host–microbe interactions at the gut lining [29]. According to a recent study, which supports this theory, the gut microbiome's components prior to surgery may have an impact on how PJI develops following a bacterial challenge [45]. It was discovered that animals with altered microbiomes were more prone to develop infections than those with unmodified gut microbiota. The "Trojan Horse" concept, a recently developed theory, postulates that blood cells other than neutrophils and macrophages may also play a role in the translocation process, acting as a "Trojan Horse" to carry pathogens that enter undetected. During periods of stress, bacteria present in the digestive system undergo phagocytosis by neutrophils within the intestines. Following this, the neutrophils traverse to distant sites of tissue inflammation, liberating their microbial cargo, leading to the initiation of metastatic infections [27,42,46]. The identification of Zonulin, a marker for enhanced intestinal permeability that is linked to soluble CD14, LPS, and other prevalent markers of inflammation and bacterial translocations, has also been a major advance in our understanding of the function of gut permeability in health and illness. Hence, when utilized together, these indicators enable the examination of gut permeability and can serve as a proxy for assessing the gut microbiome and dysbiosis. Exploiting these markers could potentially allow correlating, to some extent, impaired gut barrier function and onset of PJI [30]. Particularly, given the unfavorable outcomes that these conditions bear with them, a topic for future investigation may lie in the correlation between polymicrobial or culture-negative PJIs and gut dysbiosis. The role of antibiotics has also been investigated within the context of PJIs. Although surgeons are using chronic antibiotics more frequently in high-risk patients, it has been hypothesized that antibiotic administration disturbs the microbiota and may raise the risk of PJI [47]. This issue is further exacerbated by the fact that the duration of antibiotic prophylaxis is currently uncertain. Given that continuous antibiotic usage alters the microbiome in a host that is typically poor or immunocompromised, it may be desirable to offset the effects of antibiotics with a compound that can heal the microbiome, such as probiotics [48].

GEOGRAPHICAL DIFFERENCES

In a state-of-the-art exploration of geographical disparities in health-care outcomes [49], striking variations were found within PJI rates, with Australian and European patients exhibiting a higher prevalence compared to their American counterparts. Notably, early PJI cases within four weeks post-surgery displayed remarkable uniformity across these regions, shedding light on a potential commonality in early post-operative risks. Patients with various comorbidities and those undergoing knee arthroplasty were identified as having an elevated susceptibility to PJI. Moreover, treatment strategies reflected geographical nuances, with Australia and Europe favoring conservative approaches, resulting in fewer

initial revisions compared to the United States, while maintaining an equivalent overall surgical intervention rate. In a parallel research investigation [50], geographical influences explored to the microbial reality. Susceptibility to *Citrobacter Rodentia*, a model for enteropathogenic *Escherichia Coli* infections, was examined using germ-free mice humanized using microbiome samples from 30 donors from different countries. The intriguing discovery was that these mice exhibited varying levels of susceptibility based on the geographic origin of the donor samples. This observation was further substantiated by histological examination of colons removed 14 days after infection, which demonstrated colonic crypt hyperplasia in mice originating from the United States and Fiji, but not in those from Guatemala. Furthermore, geographical factors have emerged as influential determinants in microbiological patterns within the realm of PJI. A comprehensive, multi-country, multi-continent study [51] unveiled distinct distributions of the top ten causative microorganisms in each country, highlighting the influence of location on microbial etiology. These observations underline the intricate interplay between geography and microbiology, prompting further investigation into the underlying mechanisms that govern these disparities.

KEY ARTICLES

Here the authors propose a list of key articles that represent the progress in etiology study, diagnosis and treatment of the gut–joint axis in time (Box 1).

ESSENTIAL DIAGNOSTIC PROCEDURES

Gut dysbiosis

Factors unique to the host, including genetics, health status, and lifestyle choices, can contribute to dysbiosis. Similarly, external factors such as diet (characterized by high sugar and low fiber), xenobiotics (including antibiotics, medications, and food additives), and sanitation practices can also influence the development of dysbiosis [17]. Improved diagnostic and therapeutic approaches may be developed by gaining a more thorough knowledge of the microbiota of the gastrointestinal tract, its by-products, and its relationship with humans [53]. Tissue biopsy and other invasive diagnostic procedures are frequently required to obtain a diagnosis, determine disease subtypes, and track the course of the disease and therapy success. As a result, non-invasive and dependable indicators, such as gut microbiota species and their metabolites, are necessary and could be used as diagnostic and prognostic tools [54] (Box 2). Laboratory analysis of fecal samples have also been proposed as a non-invasive method of identifying individuals with intestinal dysbiosis [55]. Once the cultures are sampled, some specific indexes are applied to detect significant shift from the physiologic bacterial population.

One example would be largescale bacterial marker profiling, by employing 54 probes addressing 16S RNA genes (V3–V7) is able to span more than 300 bacterial markers. The dysbiosis index score that is obtained ranges from 1 to 5, with 2 indicating dysbiosis, while the scores for each taxon range from 3 to 3, with a negative number indicating reduced abundance compared to the reference population [56]. In addition, another valid technique is represented by taxon based methods. They are typically estimated using abundance ratios, abundance differences, or abundance-based linear regressions, and they are straightforward to comprehend and illustrate [56].

Periprosthetic joint infection

Standardizing the definition of PJI and establishing clear algorithms for assessing patients suspected of infection following total joint arthroplasty is crucial. This standardization helps prevent protracted and expensive diagnostic processes, as well as the unnecessary implementation of procedures that might inadvertently extend or misidentify the underlying issue [33].

Box 1

Key articles.

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Box 2

Diagnosis.

Gut dysbiosis	<i>Noninvasive</i>
	<i>Fecal analysis</i>
Periprosthetic Joint Infection	<i>Invasive</i>
	<i>Tissue biopsy</i>
Periprosthetic Joint Infection	<i>History</i>
	<i>Serologic tests (ESR and CRP)</i>
	<i>Synovial fluid biomarkers (alpha defensin)</i>
	<i>Radiologic examination</i>

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TJC: Tender joint count.

Recently, a number of useful publications have been presented in an effort to standardize the definition and treatment of patients with suspected PJIs [57]. All clinicians who treat and assess patients who have a painful total joint replacement should be familiar with these. Some among these guidelines include: The American Academy of Orthopedic Surgeons clinical practice guidelines on diagnosis of periprosthetic joint infection, The Musculoskeletal Infection Society (MSIS) modified definition of periprosthetic joint infection and The proceeding of the International Consensus Meeting on periprosthetic joint infection [58,59]. Despite the fact that there are numerous tests available to identify PJI, a comprehensive yet targeted medical history serves as the primary step in risk assessment and guides the approach for subsequent diagnostic procedures. Furthermore, unless confirmed otherwise, it is advisable to regard all patients presenting with discomfort following total joint arthroplasty as potential cases of infection [60]. Additionally, via blood work, acute-phase reactants should be identified: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be measured on all patients with a suspicion for infection as a preliminary screening tool [61]. If there is an elevation in either of these parameters or if there is a strong clinical suspicion, it is advisable to perform joint aspiration and analyze the synovial fluid. When obtaining synovial fluid, it is essential to send samples for a synovial fluid white blood cell count differential and

culture [62]. Culture represents the most accurate tool to diagnose infection but has low sensitivity and up to 20% of cases come up as culture negative [63]. While frozen segment can be useful when the diagnosis is unknown, it is highly dependent on the white blood cell threshold as well as the pathologist’s experience. The Gram stain typically yields limited information and, therefore, should not be routinely employed. The detection of infection appears to be sensitive and specific for alpha defensin and other synovial fluid indicators [62]. Finally, although it is common practice to routinely obtain plain x-rays when assessing a painful total joint arthroplasty, it’s important to note that these x-rays are seldom conclusive for diagnosing infections [60]: wide band of radiolucency at the metal–bone interface with bone destruction is a marker for the presence of infections [64]. CT scans may be useful because the presence of a periosteal response or soft tissue buildup around the site of osteolysis suggests infection. MRI shows a high degree of accuracy in diagnosing purulent infection and periprosthetic osteolysis. Nuclear imaging techniques represent another viable option: technetium-based bone scintigraphy has a high sensitivity but a low specificity since areas of higher uptake could suggest healthy bone or aseptic or septic loosening [64].

TREATMENT

Studies have found promising illness-related microbiome characteristics that have the potential to diagnose early disease stages, follow disease progression, and assess therapy effectiveness. Combination with the identification of microbiota-derived chemicals in blood, urine, or feces may improve the diagnostic and prognostic use of microbiome profiles.

The creation of effective microbiome-based medicines will also be made possible by a thorough understanding of how the microbiota and the host interact. These include altering the microbiota’s composition, such as by adding new advantageous strains or removing detrimental ones, or by transplanting the fecal microbiota to a different ecosystem to replace the existing one. Employing microbial metabolites, such as promoting or inhibiting the synthesis of certain metabolic byproducts, is another supplemental technique (Box 3).

Precise and prompt diagnosis of PJI is imperative due to the urgency associated with its treatment.

Box 3
Treatment.

Periprosthetic Joint Infection	<i>Prevention</i>
	<i>Risk factor management</i>
	<i>Preoperative antiseptic</i>
	<i>Surgical</i>
	<i>DAIR</i>
	<i>One stage revision surgery</i>
	<i>Two stage revision therapy</i>
Gut dysbiosis	<i>FMT</i>
	<i>Antibiotics</i>
	<i>Prebiotics, probiotics and synbiotics</i>
	<i>Phage-Therapy</i>
	<i>Diet</i>
	<i>Exercise</i>

FMT: Fecal microbiota transplantation; DAIR: debridement, antibiotics and implant retention.

Individualized treatment plans should be selected for each patient, and a multidisciplinary team should work together to choose the best course of action after critically evaluating the available data. For a successful therapy, a proper surgical procedure in conjunction with an antibacterial concept is essential [47].

Preventive measures should be routinely applied in order to try to prevent the onset of PJIs. The Centers for Disease Control and Prevention endorses the utilization of preoperative antiseptics [64]. Numerous skin preparation methods have been investigated, encompassing practices such as preoperative bathing, the use of antiseptic soaps, iodine-based antiseptics, and chlorhexidine gluconate-based products. Additionally, it is considered standard practice to administer intraoperative systemic antibiotics during arthroplasty procedures [65]. Antibiotic prophylaxis lowers the relative risk of infection by as much as 81% and reduces the absolute risk by 8% [66]. Furthermore, appropriate pre-operative cutaneous preparation is indicated: surgical draping, chlorhexidine-based skin preparations and clipper hair removal are worldwide standards of care exploit to decrease the rates of postoperative PJIs [67]. Furthermore, during the preoperative phase, patient optimization plays a critical role. Strong evidence supports the following measures in reducing the risk of periprosthetic joint infection (PJI): maintaining a BMI below 35, optimizing diet, achieving hemoglobin A1c levels below 7.5, keeping fructosamine levels below 292 mmol/L, quitting smoking, and conducting methicillin-resistant *Staphylococcus aureus* nasal screening [68].

As per the surgical approach, treatment strategies include surgical irrigation, debridement, antibiotic therapy, and implant retention with or without polyethylene exchange (DAIR). Other alternatives could be one-stage or two-stage revisions surgery. For early post-operative infections occurring within the first 4 weeks or acute hematogenous infections with symptom duration less than 3 weeks, the treatment of choice is DAIR [26]. Debridement involves removal of the hematoma, fibrous membranes, sinus tracts, and devitalized bone and soft tissue. In cases where symptoms have persisted for an extended duration, and a mature biofilm has formed, it becomes mandatory to undertake complete removal of the prosthesis [3]. For many years, two-stage revision surgery has been regarded as the established “gold standard” for PJI. However, contemporary literature presents data indicating comparable re-infection rates following both one- and two-stage procedures. At the same time, two-stage revision may be considered excessive treatment for a significant portion of PJI patients. Therefore, for individuals with intact or only minimally compromised bone and soft tissue, no history of previous revision surgeries, or a history of treatment with biofilm-active antibiotics, one-stage exchange has emerged as the preferred treatment option [69]. The DAIR treatment approach, while offering advantages such as

reduced invasiveness, lower technical complexity, decreased morbidity, shorter hospital stays, improved preservation of bone stock, and reduced economic burden, is best suited for specific cases [63,70,71]. The indication for DAIR treatment remains a topic of debate. This debate arises due to the varying rates of infection control reported in the literature, which range from 12% to 80% [63]. The decision to retain implants should be made considering multiple factors, including the patient's non-immunocompromised status, the presence of low-virulence microorganisms, and the successful containment of biofilm within a relatively short timeframe [70,72–75].

It is essential to acknowledge that revision surgeries pose substantial challenges for both patients and surgeons. Patients undergoing these procedures often experience multiple operations, leading to extended periods of limited mobility. Surgeons, on the other hand, confront formidable obstacles, including the complexities associated with the removal of a cemented prosthesis, the potential risk of bone loss, and the risk of injuries to peri-prosthetic soft tissues. These challenges underscore the importance of carefully weighing the decision to pursue revision surgery [70,72,76]. The one-stage revision surgery approach for PJI was introduced as an alternative to the two-stage revision surgery, particularly for chronic PJI cases. It has been reported to achieve equivalent success rates in terms of infection eradication when compared to the two-stage method. Moreover, one-stage revision surgery has demonstrated advantages such as reduced mortality and morbidity, decreased hospitalization periods, shorter durations of antibiotic treatment, and lower overall healthcare costs, making it a compelling option for select patients with PJI [77–79]. An additional treatment option is identified by the three-stage revision surgery. The first step is prosthesis explantation and a thorough debridement, together with an antibiotic-loaded cement spacer to provide local infection treatment. The second stage consists of an open biopsy and limited debridement with cultures held for at least 14 days. The final stage is completed with reimplantation of the prosthesis [80]. A three-stage revision procedure should be considered for recalcitrant microorganisms, such as staphylococci resistant to rifampicin, gram-negative bacteria resistant to ciprofloxacin, and fungal infections, owing to the absence of viable treatment modalities targeting their biofilm activity [81].

Regarding complications, comparable results have been observed for both one-stage and two-stage revision procedures in terms of re-infections and subsequent revisions [82–85]. While recent research indicates that one-stage exchange arthroplasty might offer improved outcomes, such as reduced reinfection rates and enhanced functional results, there is still a need for the establishment of clear patient selection criteria and the identification of essential elements in surgical and post-operative antimicrobial management. Failure rates after two-stage revisions have been correlated with the pre-operative presence of a sinus tract as well as infections from gram-negative bacteria [86]. It was also observed that extended wound drainage, characterized by persistent secretion for over a week, a history of prior surgical interventions for infection preceding the one-stage revision arthroplasty and the presence of *Enterococcus* infection, were identified as distinct factors that exhibited independent associations with the likelihood of undergoing repeat revision surgery after one-stage revisions [87]. Furthermore, persistent wound drainage and prior surgical procedures for infection in the affected hip were also found to be independently associated with the need for re-revision specifically due to recurrent infection [87]. Isolation of *Enterococcus* or *Streptococcus* species has also been correlated with a higher risk of failure in one-stage procedures [88].

In the authors' experience, it is standard practice to perform DAIR in the case of early post-operative acute infection (within 3 weeks). If the infection occurs after 3 weeks from the surgery, a two-stage revision is usually performed. The Protocol involves the revision, 2 weeks of intravenous bacterium-specific antibiotic followed by oral antibiotics at home for up to 6 weeks. Inflammatory markers are routinely monitored. Reimplantation follows. For culture negative infections, empiric antibiotic therapy is usually started in the absence of contraindications. In light of

these considerations, the authors continue to advocate for a case-specific monitoring approach, emphasizing the importance of maintaining a multidisciplinary, patient-centered approach for each individual case.

In the context of revision exchange procedures, there has been considerable recent discussion about the markers responsible for guiding reimplantation decisions. Currently, the standard approach involves utilizing the normalization of inflammatory markers such as ESR and CRP to determine the successful elimination of infection. Nevertheless, while these parameters are frequently considered in the presence of an antibiotic cement spacer, a recent systematic review has indicated their limited sensitivity [89]. Alternative methods such as tissue culture, synovial fluid PMN%, and synovial fluid culture have exhibited promising outcomes in the context of guiding reimplantation [89]. However, due to the limited number of studies available for each of these methods, it remains challenging to definitively recommend one as superior to the others. Effective and precise antimicrobial treatment must complement the surgical removal of the pathogen [90]. In the context of treating PJIs, the category of difficult-to-treat (DTT) pathogens assumes a critical role. These pathogens are distinguished by their lack of highly bioavailable oral antimicrobial agents [91–93]. Included in this group are *Propionibacterium* species, *Staphylococcus* species resistant to rifampin, and *Enterococcus* species resistant to aminopenicillins. These pathogens have been linked to notably poorer outcomes in terms of both clinical infection resolution and definitive infection resolution [94]. For or all surgical procedures, a total duration of antibiotic prophylactic treatment of 12 weeks is recommended [95]. In cases of persistent PJI following surgical debridement, chronic antibiotic suppression is considered an appropriate treatment approach. This option is particularly indicated for patients who either decline or are unable to tolerate further surgical interventions [59]. However, the role of antibiotics has been a topic of ongoing investigation. Given the unfavorable outcomes associated with culture-negative PJI, it is imperative to exert every possible effort to identify the infecting organism before initiating any surgical or pharmacological interventions. A commonly held belief was that the premature administration of antibiotics might compromise the yield of microbial cultures. However, several studies have provided evidence that the perioperative administration of prophylactic antibiotics does not have an impact on culture yield. Despite this empirical evidence, the International Consensus Meeting on PJI recommends that the mandatory withholding of antibiotics is not warranted. Instead, the decision to use prophylactic antibiotics in cases where PJI is diagnosed or suspected, and a specific pathogen has yet to be identified, should be based on clinical judgment, as it is currently performed by the authors. Uniformity in the duration of postoperative antibiotic regimens is lacking across the literature due to the adoption of diverse protocols. Furthermore, certain articles incorporated in published studies omit the specification of the duration of intravenous antibiotic regimens, instead presenting a comprehensive timeline inclusive of both intravenous and oral antibiotic suppressive phases. The introduction of oral suppressive antibiotics subsequent to intravenous administration introduces a significant confounding variable within both DAIR procedures and revision arthroplasties. The transition from intravenous to oral regimens in most instances is not contingent upon any predetermined temporal threshold, but rather predicated upon a blend of favorable clinical response and the availability of antibiotics with commendable oral bioavailability. Also, although chronic antibiotics are being increasingly exploited in high-risk patients, it has been suggested that the use of antibiotics interferes with the physiological microbiome and could raise the risk of PJI [96,97]. This concern becomes more apparent when we consider that the optimal duration of chronic antibiotic prophylaxis remains uncertain. Moreover, given that chronic antibiotics can have an impact on the microbiome, especially in individuals with compromised immune systems, it might be beneficial to counteract the effects of antibiotics with a microbiome-restoring agent like probiotics [98]. Additionally, it has been demonstrated that disruption of the gut microbiome correlates with reduced systemic response to PJI, demonstrating how altering the gut

microbiota can affect the development of PJI by modifying the host's response to bacterial challenge [45]. However, additional research is necessary to confirm these early results and identify the precise mechanisms at play.

The link between the gut microbiome and PJI is appealing because the microbiome can be altered and may therefore be a target for preventive therapies. As it is thought to be effective at reducing the negative effects of oral antibiotics on beneficial microorganisms, replenishing the microbiome may become normal postoperative care in order to promote the restoration of a healthy microbiome after surgery [45]. Interventions that either directly target gut microbes as well as interventions that modify the composition and function of the commensal microbes represent an innovative and potentially successful field to be explored [99].

Diet is known to have a relevant impact on the gut microbiota. Dietary nutrients may influence the gut microbiota by changing its composition, metabolism, and immunological responses, as well as its microenvironment [100]. Also, probiotics and prebiotics have been shown to be safe and beneficial dietary supplements that act by modulating the gut microbiota of the host by directly or indirectly benefiting the growth of beneficial bacteria [101]. Additionally, some therapeutic approaches combine probiotics and prebiotics, forming what is known as “synbiotics.” This combination strategy aims to enhance the effectiveness of probiotics by providing them with the nutrients they need to flourish [102].

Furthermore, even in the presence of a high-fat diet, exercise has the capacity to safeguard intestinal structure and integrity while reducing systemic inflammation. This suggests that exercise can have a distinct influence on the gut microbiota that is independent of dietary factors [54].

In recent years, alternative therapeutic methods have garnered significant attention in the field of microbiome restoration and the treatment of gut-related disorders. These innovative approaches offer new avenues for addressing complex microbial imbalances within the gut. Restoring the gut microbiome, for instance through a fecal transplant, can assist to reverse disruption and support healthy microbial diversity, which is linked to resistance to bacterial assault. In particular, fecal microbiota transplantation is a medical procedure developed to address conditions associated with the gut microbiota. It involves the transfer of fecal material from a healthy donor into the recipient's distal gastrointestinal tract as a means of treatment [103].

More recently, phage therapy has emerged as a new frontier in microbiome modulation [104,105]: Bacteriophages are natural predators of bacteria and can be harnessed to specifically eliminate harmful or pathogenic bacteria in the gut. By introducing bacteriophages that are matched to the target bacteria, it is possible to reduce the population of these harmful microbes, allowing for a shift towards a healthier microbial community. Phage therapy is particularly promising due to its precision and the ability to target specific pathogens while leaving beneficial bacteria unharmed.

Also, “bacteriophage-containing cocktails” is an evolving area of research that explores the use of carefully curated mixtures of bacteriophages [106]. These cocktails are designed to target multiple bacterial species simultaneously, making them potentially effective against a broader range of pathogens. By combining various phages with specific antibacterial properties, researchers aim to create powerful tools for combating complex microbial imbalances. This technique has the advantage of being adaptable and customizable based on the patient's unique microbiome composition.

Finally, an intriguing but relatively unexplored approach involves the use of predatory bacteria [107]. These bacteria naturally prey on other bacteria by engulfing them. Researchers are investigating the potential of harnessing these predatory bacteria to control harmful pathogens in the gut. This approach offers a unique mechanism of action and may prove effective in specific cases of microbial imbalance.

The current evidence makes the gut an exciting and novel target in the context of PJI prevention. The role of the microbiome in PJI is an area of

research that holds significant promise and warrants further investigation. However, this raises a question for future research: is it possible to modify the microbiome of patients undergoing joint replacement so as to diminish the risk of PJI? (see Boxes 4–6).

Box 4

Key issues of patient selection.

- Compromised host immunity may lead to inferior outcomes. Consider systemic risk factors such as BMI >30, diabetes, chronic disease, neurological disorders and history of previous periprosthetic joint infection.
- Carefully monitor potential alterations of the gut microbiota. Ensure a cross-talk with the gastroenterologist, particularly regarding high-risk patients.
- Debridement, antibiotics and implant retention should always be considered for early postoperative infections in absence of contraindications.
- Deficient bone stock, compromised soft tissues, and involvement of foreign materials such as meshes or bone graft, DAIR may have higher failure rates.
- Nicotine use is strongly associated with both periprosthetic joint infection development as well as debridement, antibiotics and implant retention failure with up to a 12-fold risk of infection recurrence.
- Consider antibiotic-resistant bacteria and culture-negative infections in the choice of the antibiotic regimen. Culture-negative infections have yielded significantly poorer outcomes in failed hip and knee arthroplasty.

Box 5

Major pitfalls of PJI treatment.

- Delayed diagnosis
- Incomplete synovial fluid analysis
- Inadequate periprosthetic samples for bacterial culture
- Culture negative infections
- Insufficient debridement
- Incomplete exchange of implants
- Lack of multidisciplinary approach

Box 6

Tips and tricks.

- Preventive measures:
 - Bathe patients with chlorhexidine gluconate
 - Maintain strict sterility by changing gloves and blades
 - Emphasize surgical site irrigation with diluted povidone
- Medical history: screen for past infections and potential gut-targeting conditions, as they could increase the risk of PJI
- Prompt intervention: aim for a short duration between infection and treatment, ideally within two weeks.
- Surgical intervention: employ open arthrotomy, extensive debridement, and modular component exchange when feasible.
- Tailored antibiotic therapy: customize antibiotic regimens based on the specific infecting organism.
- Duration of antibiotics: typically, six to eight weeks suffice; prolonged regimens do not necessarily yield better outcomes.
- Employ a multidisciplinary approach: collaborate with infectious disease specialists, microbiologists, gastroenterologists and orthopedic surgeons for a comprehensive treatment plan.

FUTURE PERSPECTIVES

Growing evidence suggests that the gut microbiota plays a crucial role in affecting the outcomes of surgical interventions as well as in implant survival rates. As the goal is to decrease the frequency of, possibly, the most devastating complication of total joint arthroplasty, PJI, this research sheds light on the connection between the gut microbiome, the immune system, and the potential impact of gut microbiome alterations on a patient's susceptibility to developing periprosthetic joint infection.

Therefore, the incidence of dysbiosis and microbiome alterations in patients with PJI needs to be further evaluated: clinical studies aimed at quantifying the gut microbiome within specific patient populations are essential. These studies are necessary to evaluate the potential efficacy of interventions based on the microbiome for addressing orthopedic conditions. Also, future studies should explore the mechanisms by which microbiome dysbiosis affects joint health and implant survival, as well as identify potential biomarkers or therapeutic targets for PJI prevention or management. Upon attaining a more comprehensive comprehension of the mechanisms that establish the connection between the gut microbiome and musculoskeletal tissues, it will be possible to develop appropriate microbiome-based interventions. If demonstrated to be a significant factor, developing treatments for dysbiosis may represent a novel frontier in the prevention of PJIs. As microbiome-targeting therapies hold great promise, ongoing research is necessary to refine these methods, establish safety and efficacy, and determine the most appropriate use cases for each approach.

Authors' contributions

Conceptualization, U.G.L., N.C.B. and S.A.; methodology, B.B., A.L.; software; validation, U.G.L., N.C.B., S.L. and S.A.; formal analysis, S.A.; investigation, N.C.B.; data curation, S.L.; writing—original draft preparation, B.B., A.L.; writing—review and editing, N.C.B., S.L. U.G.L.; visualization, N.C.B.; supervision, U.G.L.; project administration, U.G.L. All authors have read and agreed to the published version of the manuscript.

Funding

No external Funding was used.

Informed consent

Informed consent was obtained from all participants.

Declaration of competing interest

The authors U.G.L., A.L., B.B., S.A., declare that they have no competing interests.

One of the authors, S.L., receives royalties from Stryker, and sits on the editorial board of JBJS.

One of the authors, N.C.B., receives payment or benefits from DePuy Johnson & Johnson, and Zimmer Biomet, and sits on the editorial board of CORR, JISAKOS, and Arthroplasty.

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