G26: Does the Use of Probiotic Agents Have Any Role in Preventing Surgical Site Infection (SSI)/Periprosthetic Joint Infection (PJI) After Major Orthopedic Surgery?

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Response/Recommendation:
Probiotic agents may play a supportive role in preventing surgical site infections (SSI) and periprosthetic joint infections (PJI) after major orthopedic surgery by modulating the gut microbiota, enhancing immune responses, and mitigating microbial dysbiosis.

Level of Evidence: Weak

Delegate Vote:

Rationale:
The gut microbiome's role in systemic immunity has garnered significant attention due to its influence on systemic inflammation, infection susceptibility, and postoperative recovery. Dysbiosis, or an imbalance in gut microbiota, has been specifically linked to systemic immune dysfunction, which may exacerbate susceptibility to PJIs in these patient populations. Additionally, emerging evidence from studies measuring markers of gut permeability, such as Zonulin and soluble CD14 (sCD14), indicates that compromised gut barrier integrity may be a critical mediator in PJI development.[1]

Disruption of the gut microbiota, or dysbiosis, has been identified as a critical risk factor for infections, including periprosthetic joint infections (PJIs). A preclinical mouse model demonstrated that animals with altered gut microbiota experienced a 73% higher infection rate compared to controls, which had a 50% infection rate. This underscores the essential role of the microbiota in immune modulation and infection resistance. Dysbiosis resulted in weakened systemic immune responses, marked by diminished macrophage activity and impaired production of inflammatory mediators crucial for pathogen clearance. In contrast, mice with intact gut microbiota exhibited robust immune responses, including effective macrophage recruitment and cytokine production, which reduced infection rates by over 20% compared to dysbiotic mice.[2]

Dysbiosis has also been linked to increased gut permeability, facilitating the translocation of microbial products such as lipopolysaccharides (LPS) into systemic circulation. Elevated LPS levels can induce chronic low-grade inflammation, characterized by heightened IL-6 and TNF-α levels, which impair perioperative immune function. A recent prospective cohort study revealed that Zonulin, a marker of gut permeability, was significantly elevated in patients with PJI compared to those undergoing aseptic revision (7.642 ± 6.077 ng/mL vs. 4.560 ± 3.833 ng/mL; $p < 0.001$). This finding highlights a association between gut barrier dysfunction and increased PJI risk, emphasizing the need for targeted strategies to maintain gut integrity in susceptible patient populations.[3]

Surgical interventions can disrupt gut microbiota, leading to dysbiosis. A meta-analysis of gastrointestinal surgeries demonstrated a postoperative reduction in beneficial bacteria (Lactobacilli and Bifidobacteria) alongside an increase in potentially pathogenic species

(Pseudomonas, Enterobacteriaceae, Staphylococcus, and Enterococcus). Notably, patients receiving synbiotic or probiotic therapy had lower rates of postoperative infections and a faster restoration of gut microbiota balance. These findings align with emerging orthopedic research suggesting that preserving gut microbiota integrity may help mitigate systemic inflammation and infection risk, reinforcing the potential role of probiotics as adjunctive therapy in PJI prevention.[4]

The gut microbiota is integral to maintaining systemic immune homeostasis. Dysbiosis, or the disruption of this balance, can lead to bacterial translocation, systemic inflammation, and impaired immune responses, thereby increasing the susceptibility to PJI. A major contributor to dysbiosis is prolonged antibiotic use, which has been shown to reduce microbial diversity by up to 50%, particularly affecting key commensal bacteria such as Lactobacillus and Bifidobacterium. This loss of beneficial microbes disrupts protective mechanisms, including the competitive inhibition of pathogens and the modulation of inflammatory responses, leaving the host more vulnerable to infections.[1,5–8]The "Trojan Horse" hypothesis further elucidates this process, proposing that gut-resident bacteria, such as Staphylococcus aureus, can translocate to distant sites via immune cells like neutrophils. These bacteria utilize immune cells as vectors, facilitating their migration to prosthetic joint areas and contributing to the development of PJI. Additionally, increased gut permeability exacerbates this issue by allowing microbial products, such as lipopolysaccharides, to enter systemic circulation. This triggers a pro-inflammatory state that weakens immune defenses at surgical sites, highlighting the need for strategies aimed at preserving gut microbial integrity in at-risk populations.[1]

Preclinical studies have demonstrated that specific probiotic strains, such as *Lactobacillus rhamnosus* and *Bifidobacterium breve*, can reduce systemic inflammation and enhance local immune responses, both of which are crucial in mitigating the risk of PJI.[9–11] Murine models revealed that animals receiving probiotics experienced a 40% reduction in bacterial colonization on implant surfaces. [12,13] Furthermore, probiotic-treated mice exhibited increased levels of anti-inflammatory cytokines such as IL-10, which not only improved infection outcomes but also enhanced resistance to biofilm formation. [14] These findings suggest the potential for probiotics to serve as adjunctive therapies in reducing PJI risk by modulating both systemic and local immune responses.

Although clinical data specific to PJI remains limited, studies in broader surgical contexts provide compelling evidence of the potential benefits of probiotics. A randomized controlled trial demonstrated that the use of *Lactobacillus plantarum* resulted in no difference in postoperative infectious morbidity events among elective abdominal surgery patients (13% vs. 15%; p=0.74). Furthermore, no difference in bacterial translocation (p=0.82), gastric colonization with enteric organisms (p=0.42), or serial serum CRP levels (p=0.49 on POD 1; p=0.15 on POD 7) were seen between the control and intervention group (administered preoperative Lactobacillus plantarum 299v).[15]

A meta-analysis of randomized controlled trials in patients undergoing major gastrointestinal surgery (e.g. colectomy, liver transplantation, hepatectomy, pancreaticoduodenectomy) reported a significant reduction in nosocomial infections, with a 25% decrease in overall infection rates and a 30% reduction in hospital stays in groups treated with probiotics. These findings suggest a promising translational potential for probiotics in orthopedic applications, particularly in reducing

postoperative complications and enhancing patient recovery. However, these findings results should be interpreted with caution due to the reported risk of bias in the included studies.[16]

While further orthopedic-specific studies are required, these results support the integration of probiotics as adjunctive therapies to standard infection prevention protocols in surgical and orthopedic practice.

Probiotics play a crucial role in enhancing both innate and adaptive immune responses, which are vital in preventing infections associated with orthopedic implants. They stimulate macrophage activation, improve regulatory T-cell function, and promote the production of antimicrobial peptides such as defensins and cathelicidins. These actions collectively enhance pathogen clearance and reduce infection risk. [14,17–20]The interplay between the gut microbiota and systemic immune regulation has profound implications for PJI prevention. Elevated markers of gut permeability, such as Zonulin and sCD14, highlight the role of gut dysbiosis in systemic inflammation and immune dysregulation. [3] These disruptions can exacerbate susceptibility to PJIs by weakening host immune defenses and creating a pro-inflammatory environment. Targeting gut microbiota integrity through probiotics may mitigate these risks and enhance postoperative outcomes.

These mechanisms demonstrate the multifaceted potential of probiotics in reducing the incidence and severity of PJIs, providing a promising avenue for integrating gut microbiota management into orthopedic infection prevention protocols.

Despite promising findings, significant challenges remain in incorporating probiotics into orthopedic care:

- **Heterogeneity of Probiotic Strains**: The efficacy of probiotics is highly strain-specific, making it difficult to generalize findings across different contexts. For instance, while *Lactobacillus reuteri* demonstrated efficacy in reducing systemic inflammation in one trial, other strains like *Lactobacillus casei* have produced inconsistent results. [21–23] Differences in dosing regimens and delivery methods further complicate standardization for orthopedic applications.
- **Limited PJI-Specific Trials**: The majority of clinical evidence for probiotics focuses on reducing general surgical site infections, with limited data specific to PJI. There is a clear need for randomized controlled trials directly targeting total joint arthroplasty patients to establish strain-specific benefits and safety profiles.
- **Risk of Probiotic Use in Vulnerable Populations**: Immunocompromised patients, including those with advanced age or comorbidities common in orthopedic populations, may face rare but serious risks associated with probiotic use, such as bacteremia or endocarditis. Case reports have documented instances where even well-characterized strains translocated to systemic circulation, emphasizing the need for careful patient selection and monitoring. These risks highlight the importance of balancing the potential benefits of probiotics with the safety concerns unique to vulnerable populations.[24,25]

Addressing these challenges through rigorous, targeted research and improved standardization will be essential for translating the benefits of probiotics into routine orthopedic practice.

Conclusion:

Emerging evidence suggests that probiotics could play a role in preventing PJIs by enhancing immune function, reducing biofilm formation, and restoring microbial homeostasis. Preclinical and limited clinical data highlight their potential, but robust, large-scale studies focused on orthopedic populations are needed. The role of gut permeability, as evidenced by elevated Zonulin and sCD14 levels, further underscores the gut-immune-joint axis as a critical area for future research. However, clinical data in orthopedic patients remains limited. Well-designed randomized trials are required to further delineate the utility of probiotics for SSI and PJI prevention following major orthopedic surgery.

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