G25 – Does gut microbiome have a role in the development of Surgical Site Infection (SSI) and/or Periprosthetic Joint Infection (PJI) in patients undergoing major orthopedic surgery?

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Response/Recommendation:
The gut microbiome contributes to the development of surgical site infections (SSI) and periprosthetic joint infections (PJI), particularly in patients with known gut dysbiosis (e.g. inflammatory bowel disease [IBD] or prior *Clostridium difficile* infection).

Strength of recommendation: Limited

Delegate Vote:

Rationale:

SSI and PJI are multifactorial complications influenced by various perioperative factors[1–3]. Despite advancements in prevention strategies, infection rates have not declined much, if at all, underscoring the need to reexamine our current understanding of the causes of SSI. In recent years a large body of evidence has emerged implicating patient's own endogenous sources of microbes (nose, oral cavity, skin and the gut) in majority of SSIs [4–11]. The role that gut microbiota may play in causing SSI and PJI has been investigated in particular [12–16]. The gut microbiome is a diverse microbial community unique to each individual which begins colonization at birth and varies based on ethnicity, diet, and environment, plays a critical role in maintaining normal physiological functions and immune defense mechanisms against external pathogen through immune mediators, regulatory hormones and Short-chain fatty acids [17–29]. Recent studies indicate that the largest immune organs are the lymph nodes, bone marrow and spleen. However, the gastrointestinal tract contain around 70% of the plasma antibody-producing cells in our body which plays a major role in the humoral immune system [30–35].

Dysbiosis, defined as a disruption in microbial balance, reduces diversity and depletes protective commensal species. This state has been associated with compromised gut barrier function, increased gut permeability, and an increased the risk of infections caused by pathogens such as *Staphylococcus aureus*, Enterococcus, and Proteus [36] . Dysbiosis has been associated with diseases such as inflammatory bowel disease and *C. difficile* infections [15,37,38] and may arise from after prolonged antibiotic use or unhealthy dietary habits, both of which disrupt normal gut physiology [34–39].

Apart from a well-known causes, such as local contamination, hematogenous spread, and adjacent infections [45], emerging evidence suggests that gut dysbiosis could also contribute to SSI and PJI. Preclinical studies support the hypothesis that gut dysbiosis may enable bacterial

translocation from the gastrointestinal tract to distant surgical sites either through hematogenous spread independent of immune cell or via transport by immune cell such as neutrophils and macrophages [15,46–48]. One proposed mechanism for immune-mediated microbial transport is the "Trojan Horse" hypothesis, where microbial components cross the cell membrane of immune cells, survive intracellularly in cytosol, and are transported to sites of inflammation, such as the surgical site, where they may be released and contribute to infection[47–51]. While this hypothesis remains under investigation, it underscores the potential role of the gut microbiome in influencing post-surgical infections [50,52,53].

To investigate the potential association between gut microbiome and orthopedic infections, a systematic review was conducted. Using the appropriate MESH terms developed by librarians, we conducted a search in Medline, Embase, Cochrane Library, Scopus and identified 237 reference lists of relevant studies from inception to December 2024. After screening and removing 66 duplicates, 14 studies met the inclusion criteria for full review and data extraction.

Levast et al. identified a significant reduction in gut microbiome diversity, increased mucosal inflammation, and higher gut permeability markers in patients receiving prolonged antibiotic treatments for bone and joint infections [54]. Chisari et al. conducted a match-paired cohort study of 608 patients, showing that IBD patients were more likely to experience PJI or aseptic loosening post-arthroplasty. Their prospective cohort study further revealed elevated levels of Zonulin and soluble CD14 in PJI patients, indicating compromised gut barrier integrity[14,55]. C.difficle infection is known to be associated with poor patients outcome and increased risk of 90-days readmission and complication after THA [56]. Deckey et al. demonstrated an increased risk of PJI in patients with *C. difficile* infections within two years prior to THA, reinforcing the connection between prior gut dysbiosis and complications [57]. These findings collectively suggest that dysbiosis compromises immune function and gut permeability, increasing susceptibility to surgical infections, though definitive clinical studies remain limited.

Currently, several ongoing RCTs aim to explore the relationship between gut microbiome and SSI/PJI. International joint center (IJC) at Acibadem Hospital University is conducting studies (NCT06791993) to evaluate the impact of prebiotic/probiotic on gut microbiome following exposure to routine prophylactic antibiotic for surgery. Sharma et al. are investigating the effect of prebiotics on the gut microbiome in PJI patients that planned for a two-stage revision surgery [58]. Additionally, the GUMBO study in Canada (NCT06371950) aim to examine the relationship between gut microbiome patient's outcome, implant migration and bone density. Moreover, the AI-TKA study in Italy (NCT06634654) aims to build predictive models for post-TKA outcomes based on structural, genetic, biomechanical, clinical, psychological, biological, stress-related, inflammatory, gut microbiome and demographic data. Meanwhile, Abdeen et al. from Boston Medical center (NCT06636669) are conducting a RCT to assess the impact of administering probiotic for 6 weeks after revision surgery for PJI, focusing on infection rates.

Defining gut dysbiosis and monitoring gut barrier integrity in clinical studies remain challenging due to the complexity of contributing factors and the lack of standardized indicators.

Current research often relies on measures such as the Firmicutes/Bacteroidetes (F/B) ratio, Microbial Health Index (MHI), or plasma biomarkers like Zonulin, soluble CD14, and LPS to assess gut permeability and overall microbiome health. Although no prospective clinical studies have directly established a causal link between gut microbiome alterations and SSI/PJI, existing evidence supports the hypothesis that gut dysbiosis impairs immune function and elevates infection risk.[59]

Future research should prioritize developing reliable biomarkers for defining gut dysbiosis and establishing standardized methods to investigate the effect of prebiotics or probiotics in maintain microbial diversity,[60] . A deeper understanding of the gut-immune-joint axis has the potential to provide groundbreaking insights into infection prevention strategies for major orthopedic surgery. [61–68].

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