G1: Is there a genetic predisposition to developing Surgical Site Infection (SSI)/Periprosthetic Joint Infection (PJI) after major orthopaedic procedures?

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Response/Recommendation: Yes. There may be a genetic predisposition to developing SSI/PJI following major orthopaedic procedures. However, the current recommendation is not conclusive due to the lack of high-quality studies.

Level of Evidence: Limited

Delegate Vote:

Rationale:

Periprosthetic joint infection (PJI) and deep surgical site infection (SSI) following both total joint arthroplasty and other major orthopaedic surgical interventions are multifactorial processes that involve a complex interplay between host and environmental factors. The contribution of genetic factors in the development of PJI and SSI is the subject of ongoing investigations in an attempt to address several unanswered questions, including a more thorough understanding of the specific role of epigenetics and various single-nucleotide polymorphisms (SNPs) on the risk of developing PJI. Furthermore, while it has become increasingly clear that there may be genetic factors associated with an increased risk of PJI and SSI, the role of genetics in the context of other known risk factors has yet to be determined.

Large population-wide studies have shed light on the heritable nature of both PJI and SSI and have helped identify genes and SNPs associated with an increased risk of infection.[1–3] Anderson et al. assessed 66,985 patients who underwent either total hip arthroplasty (THA) or total knee arthroplasty (TKA), of whom 1,530 (2.3%) developed a subsequent PJI.[1] First-degree relatives of patients who developed a PJI were approximately twice as likely to also develop a PJI (hazard ratio [HR] 2.16; 95% CI 1.29 - 3.59). Furthermore, these authors identified 116 high-risk familial pedigrees that had greater than twice the likelihood of developing a PJI compared to the population average. However, these authors did not identify any specific genes associated with the increased risk they observed. Chen and Wen assessed 19,767 TKA patients, of whom 269 (1.4%) developed a subsequent SSI, and performed a genome-wide association study (GWAS) to identify SNPs associated with SSI.[2] The authors identified four SNP genotypes associated with an increased risk of postoperative infection involving four genes: PLCB1 (OR 2.67; 95%-CI 1.83-3.89), EXD3 (OR 2.42; 95% CI 1.71 - 3.42), SAMD4B (OR 3.50; 95% CI 2.14 - 5.73), and STAG1 (OR 1.86; 95% CI 1.45 - 2.38). Guo et al. performed an extensive GWAS analysis comparing 957 PJI patients to 398,708 controls and identified two high-risk SNPs and one high-risk gene (i.e., RBM26).[3] However, the two SNPs were not associated with any specific genes, and the authors did not report an odds ratio or hazard ratio associated with RBM26. Population-wide data to date suggest the risk of PJI and SSI is heritable, at least in certain subpopulations, and that there are certain SNPs associated with the development of both PJI and SSI.

Case-control studies have also elucidated specific genetic risk factors for both PJI and SSI.[4–10] However, many of these studies suffer from critical limitations, including non-generalizable patient populations, small sample sizes, and other methodological flaws such as the absence of a unified definition of PJI. Malik et al. compared 71 THA patients who developed a deep infection to 150 controls who had a well-functioning THA and found an increased frequency of the OPG-163 SNP among infected patients, suggesting "deep infection [following] THA may be under the influence of susceptibility genes."[4] Malik et al., in a separate study, compared 71 infected THA patients to 150 controls and assessed four SNPs in the Mannose-Binding Lectin gene and found one of the SNPs to be more prevalent in the infection group.[5] Navratilova et al. compared 112 TJA patients who had a PJI to 245 TJA patients who did not have a PJI and 196 control patients who did not have a TJA.[6] The authors found an SNP in the promoter region of the MBL2 gene associated with an increased risk of PJI. Stahelova et al. compared 89 PJI patients to 214 patients who did not have a PJI and 168 controls who did not have a TJA and found an SNP associated with the IL-1β gene to have an increased frequency among PJI patients, implicating this genetic variant as a potential risk factor for PJI.[7] Neufeld et al. assessed 23 THA patients with a PJI to 26 control patients matched by age, sex, body mass index, and comorbidities.[10] The authors identified three HLA genotypes associated with the development of PJI and a fourth HLA genotype that may be protective of PJI. While case-control studies have identified several genetic factors associated with an increased risk of PJI, these findings require further validation in large-scale prospective studies using standardized definitions of PJI to establish correlations and confirm their clinical relevance.

Conclusion: Based on the available literature to date, there is evidence to suggest a genetic predisposition to developing SSI and PJI following major orthopaedic procedures. However, conclusive evidence is lacking, as studies are critically limited by heterogeneity, small sample sizes, methodological flaws, and poor-quality data. Furthermore, the contribution of genetics, in the context of other known risk factors, has not been conclusively established.

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