G93: Should immune status of patients with orthopaedic infections be evaluated?

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Recommendation: There is insufficient evidence to support routine assessment of immune status of patients with orthopedic infections. However, studies to evaluate the immune status of some infected patients, such as those with multiple failures and immunocompromised status may be justified.

Strength of Recommendation: Moderate

Delegate vote: % Agree,% Disagree, % Abstain

Rationale:

The incidence of implant-related orthopaedic infection is increasing in concordance with the increased number of arthroplasty procedures occurring annually. This is in part due to the aging population and advancements in modern prosthetics.[1] However, while surgical technology has advanced, we still lack definitive means by which to identify, characterize, and manage orthopaedic infection. One target for the development of better diagnostics and interventions has been host immune status.[2] Immune markers may help diagnose infection and identify offending bacteria in PJI, as well as provide targets for preoperative optimization to prevent infection after primary arthroplasty. We reviewed 17 studies that assess how immune markers behave in the setting of orthopedic infection.

There is no gold standard for diagnosing PJI. Scoring systems like the Musculoskeletal Infection Society (MSIS) criteria and Infectious Diseases Society of America (IDSA) can sometimes yield ambiguous results, potentially leading to inappropriate or substandard treatment.[1,3,4] These current diagnostic tools include culture, serum markers (CRP, ESR), and imaging. However, some of these tests lack precision and may be expensive.[3] Using these extant diagnostic systems, complications following total joint arthroplasty, such as PJI and non-infectious arthroplasty failures (NIAF), can be difficult to distinguish.[1,3] Inclusion of immune biomarkers and synovial proteomic analysis could improve diagnostic yield in these settings. For example, Fisher et al demonstrated that PJI can be distinguished from NIAF via the levels of antimicrobial inflammatory proteins in the serum. Additionally, there are several checkpoint molecules (BTLA, PD-1, CTLA-4) that are significantly different between the aspirates of PJI patients and those with aseptic implant failures. Further studies demonstrate that certain serum marker combinations, such as the albumin/globulin ratio and CRP-albumin ratio, offer a highly sensitive way to differentiate between high and low grade PJI.[5] Gedbjerg et al. demonstrated that supplementing CRP testing with Anti-Gmd IgG titers can improve diagnostic sensitivity among staphylococcus species and identify MRSA even in culture-negative cases.[6] Using immunoassays to measure IgG levels has also shown promise in differentiating between types of orthopedic complications such as osteomyelitis and PJI. These measurements could be used for diagnosis, but also for monitoring a patient's ability to clear infection.[7,8] These examples underscore the potential for adding immune marker testing to improve diagnostic precision and treatment plans for orthopedic complications.

Biofilms play a critical role in the formation of implant associated infections. The most common pathogens are Staphylococcus and Streptococcus species. Certain strains of S. epidermidis and S. aureus have greater biofilm-forming capacity than other strains.[2,9] Biofilms can disrupt cell-mediated immunity and modify neutrophil function in favor of their formation. Many studies have demonstrated that biofilms decrease CD3+ T cells, CD4+ T helpers, and CD8+ T suppressors.[2,4,9,10] Additionally, biofilms may induce monocyte myeloid-derived suppressor cells (MDSCs), which are increased in PJI patients. Since these cells have a immunosuppressive role, medically targeting them may have a therapeutic role in the future.

Al-Ishaq et al postulated that immune markers such as C5a may be useful in distinguishing between types of biofilms in PJI.[11] Some biofilms require polysaccharide intercellular adhesin (PIA) to grow on prosthetics. This is important because some PIA expressing biofilms are more effective in immunosuppressed patients. It was found that C5a levels may be able to differentiate between PIA-dependent and independent biofilms, potentially leading to improved diagnostics and treatment specificity. Understanding how biofilms impact immunity underscores the importance of immune surveillance for future diagnostic or therapeutic studies.

Many host conditions such as rheumatoid arthritis, seronegative arthropathies, and HIV lead to immune dysregulation and increased PJI risk.[2] In addition, Conway et. al recommends assessing for immunological deficiencies preoperatively, as low immunoglobulins were strongly associated with reinfection risk.[12] There is also an association between Vitamin D deficiency and PJI.[13,14] It is well known that Vitamin D plays a significant role in bone health, but it also has been shown to modulate the immune system in favor of preventing infections. This suggests that testing vitamin D levels prior to elective orthopedic procedures would help quantify a patients risk of developing infection. Further randomized control trials need to be conducted as causality cannot be established.

Evaluating a patient's thyroid function may also prove to be efficacious as hypothyroidism is linked to impaired immune function. Addressing thyroid imbalances prior to surgery may help prevent future PJI.[15] Similarly, it may also be worth assessing a patient's nutritional status via albumin to determine a patients' ability to fight infection prior to receiving an orthopedic surgery.[16] Overall, more research must be done to determine the best way to evaluate a patient's risk for PJI, including genetic testing for alleles linked to increased susceptibility.[17] Drawbacks to immune system profiling include high cost and logistical challenges. Limited access to advanced tests may impede the ability to develop universal protocols and identifying patients who would benefit from testing remains a challenge.

Conclusion: Patients' immune status may impact the diagnostic accuracy and risk of developing PJI. Unfortunately, of the extant studies, there are limited prospective analyses and therefore no clinical consensus can be made as to the best immunologic markers for assessing infection. Surgeons should consider immune status of patients prior to indicating for primary TJA to minimize the risk of infection.

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