Authors: Christopher E. Pelt, Li Cao, Lidong Wu, Laura Certain, Michael B. Anderson, Jeremy M. Gililland

QUESTION 2: Are there any genetic factors that predispose patients to surgical site infection/periprosthetic joint infection (SSI/PJI) or predict the success of the treatment for SSI/PJI?

RECOMMENDATION: The evidence suggests a potential heritable predisposition is possible, but there is a lack of definitive evidence supporting specific genetic risk factors for SSI/PJI after total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

It is hypothesized that individuals may be susceptible to SSIs and PJIs owing to patient-related genetic characteristics. This situation may result from polymorphisms in genes encoding various proteins, receptor intracellular signaling mediators, cytokines, and enzymes vital to the functionality of the host's immune system.

In hopes of allowing for early targeted prevention in high-risk patients, risk calculators have been developed to identify patients at greater risk for developing infection following TJA. However, it has been suggested that these scoring systems are limited in their ability to accurately identify individuals at high risk and very few of them have been externally validated [1,2]. Kunutsor et al. reported that none of the risk scores they reviewed underwent subsequent impact studies to determine their utility for clinical decision-making [2]. Thus, other methods of early identification are needed in order to influence clinical decisions.

Genetic susceptibility testing has broadening interest as a means to identify patients at high risk for infection [3], specifically PJIs [4]. However, such a test has yet to be developed and implemented in the arthroplasty arena. When evaluating the immune response to mycobacterial infections, Blischak et al. reported that the innate immune system may play a role in bacterial infections [5]. Evaluating patients with multiple TJAs, Bedair et al. suggested that some patients may be at greater risk for infection due to subclinical immune deficiencies [6]. In 2013, a large population-based study by Lee et al. reported familial susceptibility to SSI which included, but was not limited to, PJI [7]. Similarly, Anderson et al. demonstrated familial clustering in TJA patients who suffered a PJI [8]. They were able to show an increased risk of PJI following TJA in relatives of patients who have experienced a PJI [8]. These families demonstrated infection rates of 9 to 17% compared to rates of approximately 2.3% in relatives of patients without PJI. Given the current literature, a heritable risk for PJI seems reasonable.

Regarding specific genetic factors, recent reports suggest that genetic variants associated with mannose-binding lectin (MBL) may be associated with an increased risk of infection in general [9,10] and in PJI populations specifically [11,12]. Burgner et al. also reported on several candidate genes identified in the literature that may be related to innate immunity [3]. For example, they noted the association of toll-like receptor (TLR) genes, *TLR2* and *TLR4* and bacterial infections [3]. Sutherland et al. performed a genetic association study on patients admitted to an intensive care unit who had evidence of infection [13]. Ultimately, they reported that the CD14, *MBL* and *TLR2* polymorphisms were associated with a greater prevalence of infection in critically ill adults. However, others report no association between the CD14 polymorphism and the incidence of infection [14]. Agnese et al. were, however, able to associate the *TLR4* mutation with an increased incidence of bacterial infections [14]. Aside from the *MBL* mutations, the CD14, *TLR2*, and *TLR4* have been reported as not being associated with infections in the PJI literature [15]. Furthermore, a recent systematic review on the genetic susceptibility to PJI concluded that although evidence exists supporting a genetic role in PJI, no definitive conclusions can be made given the relatively small amount of data available in the existing literature [15].

In summary, despite the evidence suggesting a heritable risk for infection, there is a scarcity of robust studies providing evidence on genetic risk factors for infection. Additional evidence is needed, perhaps targeting *MBL* variants, in order to consider genetic risk factors and to identify patients at greater risk for infection. Such studies may contribute to our understanding of the pathogenesis of SSI/PJI.

Given the evidence suggesting a genetic susceptibility to SSI/PJI, it seems reasonable that genetic factors may also play a role in the treatment outcomes for infection. Early studies on the ability to predict treatment outcomes of bacterial and fungal infections were not encouraging and relied on antimicrobial susceptibility tests [16–20]. Clinical and genetic risk factors for predicting treatment response has been reported for a variety of diseases [3,21–23]. Furthermore, recent studies evaluating the treatment response in patients with hepatitis and human immunodeficiency viral infections suggest that pre-treatment genetic markers exist which could increase the understanding of the patient's treatment response to anti-viral therapies [24–28]. However, there is little, if any, evidence on the ability of host genetic factors to predict treatment outcomes for surgical site or periprosthetic joint infections.

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