QUESTION 5: Can immunotherapy and immunoprophylaxis be used to prevent biofilm formation and implant-associated infections?

RATIONALE

It has been well-established that foreign body implants are a nidus for infection by biofilm-forming bacteria [1–3]. Thus, increasing host immunity against the most common pathogens associated with a particular implantation procedure is a rational approach to reduce postoperative infections [4,5]. Additionally, immunotherapy and immunoprophylaxis have been used in various surgical disciplines to prevent surgical site infections (SSI) with varying success rates [6,7]. This has also been evaluated in orthopaedics, primarily with vaccines and passive immunizations against Staphylococcus aureus, as this is the most prevalent bacteria associated with these infections [8]. Various S. aureus antigens have been incorporated into vaccines with varying levels of success [9,10]. A few investigators have also investigated antigen vaccines against Staphylococcus epidermidis [11,12].

To identify the clinical and basic science evidence to support this intervention, a systematic review was completed on the peer-reviewed literature identified by a PubMed search performed on February 8, 2018 using the key words “immunoprophylaxis or immunotherapy or vaccine or vaccination + implant + infection or biofilm.” This literature search identified 136 references from 1974 to 2018. After eliminating 56 that did not contain information directly addressing the question, the remaining 80 were divided into three categories: Primary Clinical Research (n = 5, four positive, one negative), Primary Pre-clinical Research (n = 47, all positive), and Reviews (n = 27, 25 positive, two negative).

In the specific case of cochlear implants for children, vaccination with seven-valent pneumococcal conjugate vaccine (PCV7) (Prevnar®), 23-valent pneumococcal polysaccharide vaccine (PPV23) (Pneumovax®) or both, according to the Advisory Committee on Immunization Practices (ACIP) schedules for persons at high risk, immunoprophylaxis has been indicated to reduce the incidence of pneumococcal meningitis, primarily from Streptococcus pneumoniae implant-associated infections. As summarized in a systematic review by Wei et al. [13], scientific data supports the FDA recommendation of pneumococcal vaccination for the prevention of meningitis in cochlear implant recipients. While randomized control trials have not been performed to formally establish immunoprophylaxis efficacy, the incidence of pneumococcal meningitis in children receiving cochlear implants has been reduced from that of the pre-vaccine era. Importantly, this conclusion is also supported by strong pre-clinical data demonstrating that the PPV23 vaccine protects rats from implant-associated infections following S. pneumoniae challenge via hematogenous and middle-ear routes [14].

A review of the pre-clinical literature revealed 14 primary research articles that demonstrated the efficacy of immunotherapy and immunoprophylaxis to prevent biofilm formation and implant-associated infections. The pathogens studied were S. aureus [9,15–21], Streptococcus epidermidis [11,12], Enterococcus faecalis [21,22], Aggregatibacter actinomycetemcomitans [23], and S. pneumoniae [14]. However, translating this research to human subjects remains a challenge as evidenced by the results of several anti-S. aureus vaccines and passive immunizations that have been investigated in clinical trials [6,24]. Tefibazumab was shown to be safe in phase II trials against S. aureus bacteremia [25], but its efficacy is yet to be proven. Veronate, an intravenous immune globulin, failed to prevent staphylococcal sepsis in infants [26]. A vaccine against S. aureus IsdB failed to prevent sepsis in cardiothoracic patients and was associated with increased mortality [27]. A vaccine against types 5 and 8 capsular polysaccharides failed to show any efficacy in preventing infection in end-stage renal disease patients undergoing hemodialysis [28]. On the positive side, a vaccine against four S. aureus antigens has been shown to be safe and immunogenic in humans in phase I trials [29]. Most recently, another four-antigen vaccine has also demonstrated safety and efficacy beyond one year post-immunization in healthy volunteers [30]. This vaccine is currently being tested for efficacy in spine fusion patients and the study is expected to be completed in late 2018.

Given that (1) the acknowledged efficacy of the FDA-approved pneumococcal vaccines to reduce the incidence of meningitis in children receiving cochlear implants, (2) the experimental evidence demonstrating plausible mechanisms and in vivo proof of concept with various pathogens and animal models and (3) the ongoing clinical trials based on promising efficacy data, we conclude that immunotherapy and immunoprophylaxis can be used to prevent biofilm formation and implant-associated infections in some situations.
REFERENCES