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QUESTION 2: What immune system-enhancing strategies can be employed to reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Besides medical optimization of patients to enhance their immunity, there is some evidence demonstrating that immunonutrients (amino acids), vitamin D supplementation and passive/active immunization against *Staphylococcus aureus* may enhance immune system function, and potentially reduce the incidence of SSIs/PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 74%, Disagree: 11%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

There is a close relationship between immunity and SSIs and PJIs. Thus, the strengthening of the immune system may reduce SSIs and PJIs. The strongest rationale for immune system enhancing strategies to reduce the risk of SSIs and PJIs is that perioperative immunosuppressive therapy is believed to increase these complications. This thinking has led to empirical bundles that include stopping immunosuppressive drugs (i.e., glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) and biologic agents) before elective surgery [1]. Other investigators have concluded that while there is evidence to support the use of methotrexate perioperatively in rheumatoid arthritis patients, it remains unclear whether using anti-tumor necrosis factor (anti-TNF) medications perioperatively increases the risk of SSI [2].

Although cessation of immunosuppressive therapy prior to elective surgery has been adopted as a standard of care for the aforementioned reasons [3,4], there are no data from randomized, double-blind controlled clinical trials available to guide immunosuppressive therapy in the perioperative setting [5]. Thus, to identify the available information on this subject, a systematic review was completed on the peer-reviewed literature identified by a PubMed search performed on February 24, 2018 using the keywords “immunosuppression” or “immunostimulatory,” and “SSI” or “PJI” or “elective surgery.” This literature search identified 60 references from 1992 to 2018. After eliminating 49 that did not contain information directly addressing the question, the remaining 11 were divided into two categories: Primary Clinical Research (n = 7, four studies were positive [6–9] and three studies were negative [10–12]) and Clinical Reviews (n = 4, all reviews were positive [1,2,5,13]). Of note, a review of the pre-clinical literature failed to identify any research aimed at answering this question.

Activation of the immune system by active and passive immunization is a method that has been applied for many years to cope with many infective organisms. Recently, promising studies have been conducted on active and passive immunization for *Staphylococcus aureus,* which is the main causative agent identified for PJIs [14,15]. Although a vaccine for *S. aureus* has not been introduced clinically, a clinical trial by Pfizer is underway at the moment evaluating the effect of a tetravalent vaccine on patients undergoing spine surgery. There is also the potential for the development of a vaccine against *Pseudomonas* [16,17].

The relationship between immunity and nutrients has long been studied in patients with a poor immune system. The use of glutamine, arginine, omega-3 polyunsaturated fatty acids and ribonucleic acids in the perioperative period has been reported to reduce postoperative complications [18]. In a meta-analysis conducted by Zheng et al., 13 randomized controlled trials including 1,269 patients were evaluated. The meta-analysis revealed that the addition of immunonutrients to routine preoperative diets reduced subsequent SSIs and shortened the hospital stays [19]. Moreover, immunomodulator effects of Eicosapentaenoic acid (EPA) have been elucidated [19]. In a prospective study by Horie et al., administration of preoperative arginine-enriched nutrition reduced superficial, deep and organ-space infection in a cohort of patients undergoing colorectal cancer surgery [20]. On the other hand, one study found that preoperative or perioperative immunonutrition did not reduce the postoperative infectious complications and SSIs in head and neck cancer patients [10].

Vitamin D is an important immune system enhancer, playing an essential role in neutrophil motility, activation of macrophages and inducing T-helper type 1 cells, which target bacterial pathogens that are commonly responsible for PJIs [21,22]. A recent study by Traven at al. demonstrated that low-serum vitamin D levels (25-OH) in patients undergoing joint arthroplasty were associated with an increased risk of 90-day complications as well as PJIs [23]. However, to date, no studies exist to demonstrate that correction of vitamin D deficiency repudiates the reported association. In addition, it is not known what dose and duration of vitamin D supplement are required to correct the deficiency.

Vitamin E also plays an important role in enhancing immune system function via its antioxidant properties. It also reduces apoptosis and increases macrophage activation. Chen et al. demonstrated that murine macrophages with vitamin E-enriched ultra-high molecular weight polyethylene (VE-UHMWPE) particles induced less apoptosis and Tumor Necrosis Factor (TNF) release versus particles without vitamin E [24]. Banche et al. demonstrated that VE-UHMWPE provides a less adhesive surface to *S. aureus* and *E. coli* [25]. On the other hand, Williams et al. reported that the addition of vitamin E to UHMWPE might not reduce clinically relevant rates of biofilm-related PJIs [26]. Further studies are required to better delineate the role of vitamin E in preventing PJIs.

The relationship between smoking and immunity has been established [27]. Smoking, in particular, causes immunosuppression by inactivating macrophages, neutrophils, natural killer cells and lymphocytes [27]. Moreover, smoking causes tissue hypoxia and slows blood flow to tissues potentially preventing the immune cells to reach infecting organisms in a given tissue. Smoking cessation is likely to restore immune function and potentially minimize the risk of subsequent SSIs/PJIs [28].

Greenky et al. have shown that patients with preoperative anemia (hemoglobin level less than 13 g/dL in men and 12 g/dL in women) are at greater risk of PJIs (4.3% in anemic patients compared with 2% in non-anemic patients) [29]. The association between anemia and a higher rate of SSI/PJI may be explained by numerous factors. Patients with anemia are more likely to have tissue hypoxia, which adversely affects wound healing. Patients with anemia may suffer chronic conditions such as renal disease that in their own right may be associated with SSIs/PJIs. Patients with anemia may be subjected to a higher rate of allogeneic blood transfusion with its immunomodulating effects.

Another cause of immunosuppression is malnutrition. Bohl et al. reported that patients with hypoalbuminemia are at a greater risk of developing PJIs following joint arthroplasty [30]. Malnutrition can be defined as a serum albumin level < 3 .5 g/dL, serum transferrin levels < 200 mg/dL, serum prealbumin < 15 gm/dL, and total lymphocyte count (TLC) < 1,500 cells/mm3 [31]. Dialysis therapy due to renal insufficiency, chronic hepatic insufficiency, malnutrition and depression-psychosis may cause hypoalbuminemia [32]. We should state that the current definitions of malnutrition mostly concentrate on protein deficiency, and the importance of other nutritional parameters such as vitamins, minerals, etc. are not well-studied.

This literature review also found evidence of nonspecific global health treatments that have been described as being immune system enhancing to reduce SSIs/PJIs. These include maintaining body temperature, high concentration of oxygen [13], perioperative glucose control [9] and eliminating blood transfusions [6].

With the available evidence, it is reasonable to propose that discontinuation of immunosuppressive agents, medical optimization of patients with chronic conditions, such as anemia and diabetes, and administration of immunonutrients, such as amino acids and vitamins, are likely to lead to better outcomes after surgical procedures in general and a reduced rate of SSIs and PJIs in particular. Future studies will reveal if vaccines against organisms such as *Staphylococcus aureus* are effective in reducing the incidence of SSIs/PJIs after orthopaedic and other surgical procedures.

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