1.6. PREVENTION: RISK MITIGATION, GENERAL FACTORS

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QUESTION 1: Does prior surgical site infection/periprosthetic joint infection (SSI/PJI) of a joint increase the risk of subsequent infection in another joint? If so, should elective arthroplasty of the joint be withheld in patients with active or treated PJI of another joint?

RECOMMENDATION: Yes. Prior SSI and PJI of a joint increases the risk of subsequent infection in another joint. Elective arthroplasty of the other joint should be withheld in patients with active infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Active local or systemic infections, as well as prior or current SSI and PJI of a different joint, have all been found to be associated with risk factors for developing PJI in a subsequent joint. [1–8] PJIs have been found to occur in up to 20% of patients with multiple joints in place, with one having an infection [9]. Hematogenous seeding has been thought to play an important role in this process as well as other risk factors present on the first infection.

Murray et al. [10] estimated the risk of hematogenous spread from one joint to another to be as high as 18%. Zimmerli et al. [8] identified that *Staphylococcus aureus* bacteremia increased this to up 29%. In his study, 31 patients (45 prosthetic joints) had *S. aureus* bacteremia with 13 presenting with an infected prosthetic joint. Bacterial sources were seen to be skin and soft tissue, catheters, vertebral osteomyelitis, pneumonia and contralateral prosthetic joints. Furthermore, the risk for hematogenous seeding depends also upon the patient's condition before the infectious event. The origin of the suspected remote infection plays an important role, i.e., skin infections in the lower extremities, often spread the infection by the lymphatic route rather than hematogenous. [7,11] A second study by Swan et al. [12] identified certain events, in patients with multiple comorbidities, that put them at a higher risk of suffering a PJI from a distant location, with most prevalent being recent cellulitis.

Patients having been treated for a prior PJI, have an 11% greater risk of developing a PJI in a new joint. In a study by Bedair et al. [13], the authors specifically addressed patients undergoing total joint arthroplasty after a successfully treated PJI in a previous joint. This multicenter, retrospective, case-control study included 90 patients (35 total hip arthroplasties and 55 total knee arthroplasties). They found that patients who had a history of a treated periprosthetic joint infection had a greater risk of developing a PJI in a subsequent joint (10 of 90 versus 0 of 90 in the control group) (relative risk: 21.00, $p = 0.035$). No other factors were identified to be associated risk factors for developing a second joint infection.

Abblitt et al. [14] also reviewed patients with periprosthetic joint infection and multiple prosthetic joints. A total of 167 patients were identified, out of which 76 had multiple prosthetic joints in situ. Ten patients (13%) developed a PJI in a second location and the rate of infection spreading from one joint to another was 8.3%. This was a retrospective study that reviewed infections in existing arthroplasties and did not include arthroplasties done following an existing PJI.

The data reviewed suggests that in cases of remote infections, the risk of hematogenous seeding exists. This depends also on the pathogen, being higher with infections secondary to *S. aureus*. Therefore, in the scenario of a potential or suspicion of a distant infection, the patient should be delayed for elective arthroplasty surgery until all possible sources of infection are treated. The hazard of getting a new prosthetic joint infected after a PJI at another anatomic site seems to be evident; however, the exact risk is unknown. Patient-related risk factors play a crucial role in the development of PJIs and need to be considered.

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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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QUESTION 3: For patients awaiting organ transplant who need elective arthroplasty, should the arthroplasty be done before or after the organ transplant?

RECOMMENDATION: We recommend performing arthroplasty after solid organ transplant, using normal antibiotic prophylaxis. Recent studies utilizing publicly available databases compare patients undergoing total joint arthroplasty (TJA) during organ replacement therapy (i.e., hemodialysis) versus after organ transplantation (i.e., kidney transplant) and consistently report less infections in the post-transplant cohort.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 2%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

As the number of primary and revision total joint arthroplasties are expected to increase dramatically, so too will surgical site infections (SSIs) and periprosthetic joint infections (PJIs) [1,2]. Infection is one of the leading causes of failure for primary and revision total knee arthroplasty (TKA) and total hip arthroplasty (THA) [3–5], making patient health optimization and infection prevention paramount.

Furthermore, the elderly population in western countries continues to grow, and mean life expectancy is increasing as is activity level [3]. This is possibly secondary to advances in medical care and the treatment and prevention of chronic medical conditions. As patients continue to live longer with chronic medical conditions, there has been a parallel increase in need for solid organ transplantation (SOT) for end-stage organ failure. And as SOT patients survival improves, the number of these patients undergoing THAs and TKAs is increasing. In 2015, up to 126,670 organs were transplanted globally, including 84,347 kidneys, 27,759 livers, 7,023 hearts, 5,046 lungs, 2,299 pancreases and 196 small bowels [6].

Like the general population, the life expectancy of organ recipients is also increasing, predisposing them to osteoarthritis because of advancing age and ensuing osteonecrosis from corticosteroid and anti-rejection drug administration [7–9]. Previous studies have demonstrated that both end-stage organ failure and SOT patients have good pain relief and function after hip and knee arthroplasty [10,11]. While no level I or level II studies currently exist, the timing of arthroplasty in these patients has been investigated in retrospective and database studies.

Overall, five studies were identified that compared patients receiving arthroplasties during organ arthroplasty therapy to those receiving it after SOT [12–16]. All of the studies were retrospective and investigated end-stage renal disease versus kidney transplantation. Garcia-Ramiro et al. identified a 20% infection rate (2/10) in hemodialysis (HD) patients compared to 50% (4/8) renal transplant patients [13]. In a multicenter study, Lieberman et al. found an 18.7% infection rate in HD patients (3/16) compared to 3.3% in renal transplant patients (1/30) [14]. Likewise, Shrader et al. found a 22.2% infection rate in HDs (2/9) compared to 10.7% (3/28) in renal transplants [15]. These studies combined SSIs and PJIs and lacked the power to determine if these rates were statistically different when stratified.

To compare organ failure patients with SOT patients for susceptibility to PJI after joint arthroplasty, infection risks of a non-functioning organ (and secondary disease) should be weighed against infection risks and disturbed wound healing caused by immunosuppressive medications. In addition to infection risks specific to each organ, the type of antibiotic prophylaxis and anesthetic could have a different influence on infection before or after SOT, which is hard to predict. Without large cohorts and prospective data, it is important to recognize the risks of infection for both groups.

To address the problem of small cohort studies, more recent studies have utilized large, publicly-available databases to adequately compare cohorts. Cavanaugh et al. used the Nationwide Inpatient Sample (NIS) database to compare 1,747 HD patients to 1,055 renal transplants [12]. They found that HD patients had higher rates of SSIs (odds ratio (OR): 2.92, 95% confidence interval (CI) 1.93 to 4.42, pand wound complications (OR (001. > : 2.50, 95% CI 1.41 to 4.44, p after TJA, when compared to renal transplant patients (002. = [12]. The authors advocated that renal transplantation be performed before TJA because this population may be associated with less postoperative complications and mortality compared to dialysis patients [12]. Similarly, Kildow et al. used 100% of the Medicare database to compare similar groups with THA [16]. They reported that patients on HD were at greater risk of PJI (OR: 6.61, 95% CI 4.25 to 10.27) at 90 days compared to patients with renal transplant [16]. This risk persisted at the two-year mark (OR: 4.47, 95% CI 3.66 to 5.47). Interestingly, patients who received a transplant had a similar PJI risk at two years compared to control patients who had only diabetes, but no organ failure. The authors concluded that diabetic patients with kidney failure should undergo renal transplant prior to THA, to optimize the surgical outcomes [16]. Similar conclusions for postoperative complications apply for patients with liver cirrhosis, and the first 90 days postoperatively appear to be critical for PJIs as early cases have been observed at a rate of 22.2% [17].

However, the risk for PJI following TKA, after SOT is 3.2 to 17.2%, and does appear higher than following THA [11,17–20]. After SOT the predominant reason for revision failure is PJI in 10% of THA, and 22.2% of TKA patients [21]. Causative microorganisms (staphylococci and streptococci) are overall similar to PJI in the general population, in which type of normal antibiotic prophylaxis should be sufficient [20]. The survivorship of revised THA after five years and ten years seem comparable with non-transplanted population regarding PJI as cause of failure (2 to 10%) [21,22]. However, there is an increased risk for aseptic loosening during the 10 to 15 years post-arthroplasty, hypothesized to be caused by decrease in graft function, and increase in organ failure, as well as the presence of higher medical comorbidities in this patient population. There is also another aspect to this question. Patients in need

of organ transplant who undergo TJA and develop a subsequent PJI may lose the opportunity to undergo organ transplant because of the concern for the presence of infection in the replaced joint and the possibility of a flare-up of infection when immunosuppressive drugs are administered.

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