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PROSTHETIC JOINT INFECTION (S NODZO AND N FRISCH, SECTION EDITORS)

Perioperative and Modifiable Risk Factors for Periprosthetic Joint Infections (PJI) and Recommended Guidelines

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Abstract

Purpose of Review Periprosthetic joint infection (PJI) remains a complication that is associated with high morbidity as well as high healthcare expenses. The purpose of this review is to examine patient and perioperative modifiable risk factors that can be altered to help improve rates of PJI.

Recent Findings Evidence-based review of literature shows that improved control of post-operative glycemia, appropriate management of obesity, malnutrition, metabolic syndrome, preoperative anemia, and smoking cessation can help minimize risk of PJI. Additionally, use of *Staphylococcus aureus* screening, preoperative evaluation of vitamin D levels, screening for urinary tract infection, and examination of dental hygiene can help with improving rates of PJI; similarly, appropriate management of perioperative variables such as limiting operating room traffic, appropriate timing, and selection of prophylactic antibiotics and surgical site preparation can help to decrease rates of PJI.

Summary In summary, PJI is a morbid complication of total joint arthroplasty. Surgeons should be vigilant of modifiable risk factors that can be improved upon to help minimize the risk of PJI.

Keywords Periprosthetic joint infection · Modifiable risk factors · Perioperative risk factors

Introduction

Total hip and knee arthroplasties are among the fastest growing procedures in the USA [1]. However, periprosthetic joint infection (PJI) remains a significant complication that is associated with high morbidity as well as high healthcare expenses. It has a measurable impact on all parties involved including the patient, surgeon as well as the healthcare system [2]. PJI is projected to have an economic burden in excess of 1.62 billion dollars by the year 2020 [3]. This is especially important to address since estimates currently project large increases in demand for total hip and knee arthroplasties. By the year 2030, the demand for total hip arthroplasty is estimated to grow by 174% and the demand for total knee arthroplasties is projected to grow by 673% [4]. Similar increases are expected for revisions as well [4].

The incidence of deep periprosthetic infection after primary total hip and knee replacements has been reported in the literature to range anywhere from 0.5 to 2% [2, 5]. In examining total knee revision procedures, Bozic et al. showed that infection was the leading cause of revisions comprising 25% of all failures in TKA [6]. Other studies have also reported infection to be an important reason for patients undergoing revision in the total knee population with rates ranging from 33 to 38% [7, 8]. Kurtz et al. as also shown that infection is on the rise as a reason for revisions and will continue to be the dominant reason for necessitating revisions [9, 10].

It is important that we attempt to minimize the risk factors which can play a role in the development of PJI in the setting of such alarming trends. In particular, modifying risk factors from both the patient perspective as well as in the perioperative environment can help with decreasing the overall risk of developing a PJI. Multiple patient risk factors have been identified that can be altered prior to surgery to help minimize the risk of PJI.

This article is part of the Topical Collection on *Prosthetic Joint Infection*

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Modifiable Risk Factors

Diabetes

Diabetes has been associated with increased risk of surgical site infection in a variety of surgical procedures [11, 12]. Additionally, the incidence of diabetes is continuing to rise in the USA [13]. In particular, patients with uncontrolled diabetes have been found to have an increased risk of infection of nearly 2.8 times after total joint arthroplasty [14].

Hemoglobin A1c (Hgb A1c) is frequently used as a marker of long-term glycemic control and may take 3 months to change. Patients with optimal glycemic control should have Hgb A1C levels less than 7.0. This corresponds to an estimated average glucose level of 154 mg/dL. Hgb A1c has frequently been used a routine screening test as it is a simple test which allows the provider to gain insight of the patient's glycemic control over the past 3 months [15, 16]. However, it appears that perioperative glucose levels have an increased ability to predict PJI as opposed to Hgb A1c alone [17, 18•].

Surgical stress increases the production of hormones that antagonize insulin and predispose patients to hyperglycemia. In particular, perioperative glycemic control needs to be strictly enforced as surgical stress-related post-operative hyperglycemia, even in patients without a diagnosis of diabetes, has been found to have an independent risk factor for the development of surgical site infection in a dose-related relationship [19–21]. Thus, it is recommended that blood glucose levels be maintained between 110 and 180 mg/dL in the perioperative period to help minimize the risks associated with hyperglycemia. This can be achieved with frequent blood sugar checks and initiation of diabetic management protocols in the post-operative period.

Obesity

Similar to diabetes, the prevalence of obesity has also significantly increased. Obesity has been shown to significantly contribute to a higher rate of osteoarthritis and eventual increased use of arthroplasty [22]. While studies have shown that patient satisfaction and functional improvement in the obese patient population are similar to the non-obese group, obese patients are, nonetheless, at higher risk of postoperative complications, specifically PJI [23•]. Multiple studies have correlated increased body mass index (BMI) with increased rates of wound infection [24, 25]. Malinzak et al. showed that those with a BMI > 50 kg/m^2 had 21.3 times greater odds of acquiring an infection [24].

Obesity predisposes patients to higher surgical times with increased surgical dissections needed to gain exposure. Additionally, the poor vascularization of adipose tissue further compounds this problem. Surgeons should also have a high index of suspicion for metabolic syndrome in those with obesity.

A workgroup of the American Association of Hip and Knee Surgeons (AAHKS) evidence-based committee came up with a consensus opinion that consideration should be given to delaying total joint arthroplasty in a patient with a BMI > 40, especially when associated with other comorbid conditions, such as poorly controlled diabetes or malnutrition [22].

Metabolic Syndrome

Metabolic syndrome is composed of a cluster of conditions arising from insulin resistance that impairs normal leukocyte function. It is defined as having a BMI > 30 kg/m^2 with central obesity, as well as two of the following: hyperlipidemia, hyperglyceridemia, hypertension, or diabetes [26]. Zmistowski et al. have shown increased risk of PJI (14.3 vs 0.8%) in those with uncontrolled metabolic syndrome compared to those with controlled disease/healthy cohort [27].

Malnutrition

An often-underappreciated facet of obesity involves malnutrition, or so called paradoxical malnutrition in obese patients that have high caloric but nutritionally poor diets. A prospective study evaluating the role of malnutrition in total joint arthroplasty found that malnutrition was present in 42.9% of obese patients [28]. Additionally, the geriatric population, patients with gastrointestinal problems, patients with a history of alcohol abuse, and cancer are also at increased risk of malnutrition. Multiple studies have implicated that malnutrition has a contributing factor to increasing the risk of a PJI [29, 30]. Specifically, patients with malnutrition were found to have 5 to 7 times greater risk of developing a major wound complication [31]. Malnutrition has also been associated with an increased risk of infection in patients undergoing revision total joint arthroplasty [32•].

Simple and immediately available laboratory tests can help to identify patients at risk for malnutrition. These include a total lymphocyte count of less than 1500 cells/mm^3, a serum albumin of less than 3.5 g/dL, or a transferrin level of less than 200 mg/dL [29]. Patients with pre-operative malnutrition should be encouraged to work with a dietician to improve their nutritional intake and help prepare them for the catabolic demands required in the post-surgical period.

Smoking

Smoking, and its primary offending component, nicotine, has been associated with microvascular constriction and decreased oxygen delivery to tissues [33, 34]. In particular when analyzing the effects of smoking on total joint arthroplasty, Duchman et al. reported increased risk of wound complication

with both current as well as well as former smokers in a large national database study with current smokers having higher rate of wound complications than former smokers [35, 36•]. Additional studies have also corroborated the deleterious effects of smoking as it pertains to PJI [37].

It has been shown that a smoking cessation program can help decrease complications associated with the use of nicotine even if it is introduced as late as 4 weeks before surgery [38]. Thus, it is our recommendation that patient undergoing total joint arthroplasty has a minimum period of 4 weeks of smoking cessation prior to their surgery. Smoking cessation can be confirmed via easily available laboratory test, the serum cotinine assay (normal value of ≤ 10 ng/dL) [39]. Patients undergoing smoking cessation therapy using transdermal nicotine patches continue to test positive for serum cotinine as the nicotine continues to be absorbed systemically [40, 41].

Staphylococcus aureus Screening

The prevalence of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in patients admitted to hospitals is increasing [42]. Nasal swab rapid polymerase chain reaction has allowed physicians to identify patients who are colonized. This allows for the elimination of the bacteria from the patient's nasal flora prior to surgery. Kim et al. have found that implementing an institution wide prescreening program allows for the identification of carrier status of *Staphylococcus aureus* among patients and leads to significant reduction in post-operative rates of surgical site infections [43]. Similarly, Rao et al. noted that implementation of an institutional decolonization protocol helped to decrease overall infection rate and resulted in significant economic gains for the hospital [44]. It is our recommendation that patients undergoing elective total joint arthroplasty undergo screening for *S. aureus* through nasal swabs. If they are positive, we recommend that they undergo application of mupirocin nasal ointment twice daily to both nares and bathe with chlorhexidine daily for 5 days immediately prior to the scheduled surgery. Alternatively, patients can also be treated with nasal povidone-iodine swabs which have demonstrated reduction in the colonization of *S. aureus* [45]. In addition, patients who screen positive for MRSA should also receive a single dose of vancomycin along with standard perioperative antibiotics.

Urinary Tract Infection

Urinary tract infection (UTI) is a common nosocomial infection that creates a reservoir of pathogens and increases patient morbidity [46]. Prolonged postoperative urinary catheter use has been identified as a significant risk factor for the development of UTI [47]. The role of UTI in the development of PJI, however, remains controversial. Some authors have noted the development of PJI in patients with UTI [48–50] while others have shown no association between UTI and PJI [46, 51].

It is our recommendation that if the patient has symptoms of UTI such as dysuria, urgency, frequency, etc. and has more than 1×10^3 bacteria/mL of urine, postponement of the surgery should be considered. However, if the patient is asymptomatic but has 1×10^3 or more bacteria/mL of urine, we recommend not withholding surgery but seeking to treat the UTI with a routine course of postoperative oral antibiotic.

Poor Oral Health

It has been noted in the literature that patients who have had total joint replacements practice good dental hygiene in general [52•]. However, there is a lack of literature on the role of pre-operative screening and its association with PJI. Recent studies have questioned the need to obtain routine preoperative dental screening for hip and knee arthroplasty patients [53]. In general, it is our recommendation to follow a common-sense approach. Patients should have a dental exam and clearance if they have evidence of decayed teeth, abscess, gingivitis, or periodontitis and should have routine cleanings done prior to surgical intervention.

Immunosuppression

Acquired immunodeficiency syndrome (AIDS) is a sequelae that frequently develops in patients with human immunodeficiency virus (HIV) when their $CD4^+$ T cell count falls below 200 cells per μL or when they develop specific diseases in association with an HIV infection. The literature has only small series of patients with HIV/AIDS who have undergone total joint arthroplasty with mixed results [54, 55]. Parvizi et al. reported high rates of deep infection (28.6%) in their series [55]. In this high-risk patient population, it is our recommendation that the surgeon and patient work in conjunction with an infectious disease consultant to ensure that these patients are optimized thoroughly prior to their surgical intervention. Specifically, heightened awareness should be taken in those with a CD4 count less than 200 and in those with a viral load greater than 10,000 copies/mL.

Inflammatory Arthropathies

Patients with inflammatory arthropathies such as rheumatoid arthritis and systemic lupus erythematosus are often at increased risk of post-operative infection [56, 57]. Many of these patients are on complex drug regimen that include a variety of immunomodulators. These medications often have deleterious effects on wound healing and infections. For example, tumor necrosis factor (TNF) alpha inhibitors are tremendously helpful adjuncts in the management of these diseases. However, they place patients at significant risk for

developing opportunistic infections. Momohara et al. reported patients on TNF alpha inhibitors to be at higher risk for surgical site infections [58]. A recent guideline published jointly by the American College of Rheumatology and American Association of Hip and Knee Surgeon used available evidence to make recommendations on which medications should be stopped in elective total joint arthroplasty and if withheld, when they should be restarted [59•]. In general, traditional Disease Modifying Antirheumatic Medications (DMARDS), such as methotrexate, do not need to be withheld prior to surgery. Biologicals, however, place patients at increased risk for development of PJI and should be withheld one dosing cycle prior to surgery. The medication can be re-started following surgery once surgical wounds have healed and in the absence of signs of infection.

Preoperative Anemia

Preoperative anemia has been found to increase complication rates in patients undergoing total joint replacement including development of PJI [60–62]. Additionally, correction of preoperative anemia with postoperative transfusion has been associated with increased risk of infection of up to 9% with each unit of blood that is transfused [63, 64]. This increased risk is thought to occur through transfusion-related immunomodulation [65]. It is our recommendation that patients identified as having preoperative anemia, defined as Hgb < 13 g/dL for men and Hgb < 12 g/dL for women, work with their primary care doctor in optimizing their hemoglobin levels preoperatively though adjuncts such as improved nutrition, and the use of erythropoietin prior to their surgical intervention. Additionally, the surgeon should also strongly consider the use of blood conservation tools during the procedure such as the use of tranexamic acid.

Vitamin D

Vitamin D, as measured by serum 25-hydroxyvitamin D, has long been known to play a crucial role in bone hemostasis [66]. Vitamin D deficiency, defined by a serum 25-hydroxyvitamin D concentration ≤ 20 ng/mL, is unfortunately quite common in the US population with an overall prevalence reported at 41.6% [67]. Studies have shown vitamin D levels to be severely low in patients with PJI [68, 69•]. Animal models have also shown that while deficiency of vitamin D results in increased risk of PJI, this can be reversed with preoperative repletion [69•]. Thus, it is our recommendation that vitamin D levels be obtained preoperatively and if deficient, < 20 ng/ mL, supplementation be instituted.

Perioperative Modifiable Risk Factors

Antibiotic Prophylaxis

Administration of preoperative antibiotic prophylaxis is effective in reducing rates of surgical site infections [70]. Routine prophylactic antibiotics, dosed in accordance with the patient's weight, should include a first-generation cephalosporin such as cefazolin. Patients who are allergic to beta lactam antibiotic should receive clindamycin or vancomycin. However, timing is also equally important as the choice of antibiotic. Prophylactic antibiotics should be administered ideally as near to the time of the incision as possible, but within 60 min prior to the incision for a first-generation cephalosporin or clindamycin, and within 2 h of incision for vancomycin. We recommend that weight-based dosage of vancomycin be considered for those who have been shown to be colonized with MRSA or those who had a prior infection with MRSA [71]. Additionally, we recommend that antibiotics be discontinued within 24 h after the surgical procedure.

Surgical Site Preparation

Current evidence recommends the use of chlorhexidine gluconate-based solutions for surgical site preparations and has been found to be superior to the use of iodophor-based solutions as well as other iodine ion-based solution at reducing the burden of microbes at the surgical site. Chlorhexidine gluconate acts by disrupting the cellular membranes of bacteria and is longer acting than iodophors. While chlorhexidine gluconate and povidone-iodine both reduce bacterial counts on contact, the effect is much longer with chlorhexidine [72, 73]. Additionally, iodophors can be inactivated by serum proteins and should be allowed to dry in order to maximize their antimicrobial action [72]. Alcohol is also a potent antimicrobial. However, it lacks residual activity after application. Our recommendation is the use of a combination agent that involves both chlorhexidine gluconate as well as isopropyl alcohol. Hair removal is another facet of surgical site preparation that can potentially play a role in increasing surgical site infections. We recommend that hair removal be minimized and if necessary, and that electric clippers be used rather than shavers in accordance with the Centers for Disease Control and Prevention guidelines [74].

Operating Room Environment

Several operating room variables have been studied to see if rates of infection could be decreased in total joint replacement patients. These include the use of ultraviolet light, laminar flow, body exhaust suits, etc. However, maintaining a disciplined operating room by limiting operating room traffic has been shown to decrease the rate of surgical site infections [75,

76]. Thus, it is crucial that traffic into and out of the operating room through both the sterile core as well as the common corridor be limited during arthroplasty procedures to decrease the risk of surgical site infections.

Conclusion

The well-known idiom, an ounce of prevention is worth a pound of cure, is certainly applicable to PJI. While PJI will not be completely eliminated in the coming years, surgeons should make use of available evidence-based guidelines, such as the ones proposed above, to help improve patient and perioperative modifiable risk factors to minimize risk of PJI.

Compliance with Ethical Standards

Conflict of Interest Bryan D. Springer reports board membership with AJRR and ICJR, consultancy fees from Stryker, Convatec, and Osteoremedies, lecture fees from Ceramtec, and royalties from Stryker, outside of the submitted work.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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