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Introduction

Periprosthetic joint infection (PJI) is a potential complication in any prosthetic joint, even in the absence of known risk factors. However, effective minimization of the risk for PJI requires elimination of known factors that increase the opportunity for exposure of the joint to pathogens or limit the body's ability to eliminate intra-articular pathogens. Known risk factors for PJI can be categorized into patient-related, surgery-related, inpatient postoperative, and long-term factors. While overlap of factors can occur between these groups, it is important to appreciate that the presence of these risks at any point increases the opportunity for the development of PJI. This chapter discusses the mechanism and impact of the factors that compose these groups.

Much of the information regarding risk factors for the development of infection after total joint arthroplasty comes from uncontrolled case series or small case-control studies. Since PJI is an

uncommon complication, most of the studies of adequate power represent those patients that were operated in large referral institutions. Unfortunately, these institutions represent only a minority of total joint replacement procedures that are performed [1]. Therefore, these studies may not be a precise representation of reality [1, 2]. Furthermore, disparity in the definition of periprosthetic infection in the literature is an important barrier to a clear understanding of the relationship between potential risk factors and PJI [3, 4]. When referencing this chapter and other sources, these shortcomings of the evidence should be considered.

Patient-Related Risk Factors

Demographic Factors

Age

Kurtz et al., in a national study, observed that age was a risk factor for PJI following both total knee (TKA) and total hip arthroplasty (THA) [5]. They reported a bimodal distribution, with the lowest PJI incidence in 55–74 year olds. Interestingly, Soohoo et al. observed the same bimodal distribution in another large population-based study [6]. They studied readmission for PJI within 90 days of THA and found that patients older than 75 or younger than 55 years old had significantly higher probability of infection compared with patients between 55 and 74 years old, with an odds ratio of 1.28 and 1.34, respectively. Prior to

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this, Soohoo et al. published a similar investigation among TKA patients, finding those younger than 65 years of age at increased risk for 90 day readmission for infection [7].

Using surgical site infection (SSI) surveillance service database in England, Ridgeway et al. studied the link between various risk factors and SSI [8]. They found that an age over 80 years was a significant risk factor for SSI in primary THA. The same age group demonstrated an association with SSI following primary hemiarthroplasty. However, after adjusting for covariates, age was not a significant predictor of SSI in this cohort. Similarly, some Nordic registry-based studies did not find any link between age and PJI following TKA [9–11]. Dale et al. compared three Norwegian health registries for THA and found that advanced age was a risk factor for both SSI and revision due to infection [12]. Interestingly, for hip hemiarthroplasty secondary to fracture, age less than 60 years was found to increase the probability of revision due to infection, which was explained by the fact that young patients requiring hemiarthroplasty are likely to have severe comorbidities with a shortened life expectancy [12].

Patients in the senior age group usually undergo primary arthroplasty when they are in an optimal health condition. Various studies have reported a lower mortality rate in patients undergoing THA or TKA compared to general population, possibly related to a selection bias [8, 13]. However, the selection method for young patients may be different. Many young patients who undergo total joint replacement are likely to have comorbidities that can increase their susceptibility to PJI. This is indirectly supported by the evidence provided by Lie et al [8]. They observed that 8-year mortality rates in younger THA patients (under 60 years old) were higher than the corresponding general population with the same age and gender. The opposite was seen in patients over 60 years of age. It appears that advanced age may be a risk factor for PJI. However, the link between advanced age and PJI can be confounded to a certain extent by some other risk factors such as comorbidities, lower threshold for blood transfusion or longer hospital stay. Moreover, some

studies have found a susceptibility of PJI in the youngest age group undergoing primary arthroplasty but the reason for this is yet to be exactly defined.

Gender

The prevalence of many musculoskeletal disease and infections is not similar between females and males. Sex hormones and sexual chromosome genetic content modulate both innate and adaptive immune system [14]. Therefore, the immune system of males and females may respond differently to pathogenic bacteria, possibly explaining why the prevalence of some infections is not similar between women and men. Most studies investigating whether both sexes are equally susceptible to PJI, have found that males are at greater risk compared to females [2, 5, 6, 9–12, 15–19]. Interestingly, Lubbeke et al. observed that although PJI was more common in men than in women among the non-obese population, obesity strikingly increased the incidence of PJI in women (16.1 times more compared to non-obese women). However, obese and non-obese male patients were not significantly different in terms of incidence of PJI following THA [18].

Nonetheless, some other studies have found higher rates of PJI in females and others did not observe any link between PJI and sex in total joint arthroplasty or in hip hemiarthroplasty [7, 8, 12, 20–22]. Due to these conflictive findings, some authors have not considered gender as an independent risk factor for PJI, suggesting that the difference seen between sexes is probably a proxy for some other risk factors that were not studied [23, 24].

Supporters of the link between PJI and gender have attributed this association to factors such as difference in skin and subcutaneous conditions like pH, sebum induction, skin thickness, fat distribution, and metabolism rate [25–27]. Moreover, it has been suggested that the microbial flora between males and females are different, and males have a higher likelihood for being persistent *Staphylococcus aureus* carriers [28]. Some investigators have reasoned that surgeons probably have lower thresholds for males when considering intervention or males

may have a greater chance of being referred to an orthopedic specialist by the primary physician [11, 12, 29–31].

Race

Existing evidence shows that the 90-day incidence of infectious and noninfectious complications following total joint arthroplasty (particularly knee replacement) along with mortality are generally higher among non-white racial groups in comparison with white patients [2, 6, 7, 17, 32]. All of these studies include a low proportion of non-white groups, rendering them underpowered for uncommon complications such as PJI. This may explain why they could not find any difference for PJI specifically, or why the same difference for overall infectious complications did not exist for THA [17, 32].

However, the demonstrated dissimilarity among racial groups merits several considerations. Disparity exists between races in utilization of total joint replacement that is not explained by a difference in prevalence of osteoarthritis, insurance status, or access to health care [33]. Osteoarthritis is more prevalent in African-American and Hispanic populations older than 70 years old compared with non-Hispanic Caucasians [34]. However, elderly African-Americans with osteoarthritis present later and are less likely to undergo total knee replacement than their white counterparts, even when there is no economic impediment [35, 36]. African-Americans have also been shown to have higher body mass index (BMI) at the time of TKA [36]. Non-white patients who undergo total joint arthroplasty have significantly longer length of postoperative stay than white patients, even when adjusted for comorbidities [37, 38]. Therefore, patients from different racial groups do not represent uniform perioperative conditions, and there are some potential risk factors for PJI that have been reported to be different among these groups in previous studies. However, the current evidence for association of PJI and minority groups should be interpreted cautiously since unrecognized and uncontrolled confounding factors may have contributed to this relationship.

Socioeconomic Status

Socioeconomic status is a complex factor that can potentially effect a patient's risk of PJI [6, 7, 15, 16, 39]. Theoretically, lower socioeconomic status can lead to less favorable overall health status due to poor nutritional status and suboptimal care of preexisting comorbidities—both of which are discussed elsewhere as potential risk factors for PJI. However, it can also be influenced by other confounding factors such as race. Unfortunately, the available evidence fails to address these complex associations.

Obesity

Obesity substantially increases the morbidity from osteoarthritis, and is prevalent in the arthroplasty population [40]. Associated comorbid conditions in obese patients, such as ischemic heart disease, hypertension, hypercholesterolemia, poor nutritional status, and type two diabetes mellitus or a constellation of these in the form of metabolic syndrome, delay postoperative recovery and increase the risk of perioperative complications [41–43].

A retrospective analysis has estimated a BMI over 35 kg per meter-squared (kg/m^2) increases the risk of SSI following TKA and THA by 6.7 and 4.2 times, respectively [44]. With a BMI of more than 40 or 50 kg/m^2 the odds of PJI increased 3.3 and 21 times, respectively [45]. Various factors can potentially predispose obese patients to PJI. These patients are at increased risk of postoperative surgical wound complications [46, 47]. The risk of wound dehiscence is higher due to increased surface tension at the incision site. Furthermore, extensive dissection during surgery may be required which may increase the risk of hematoma formation, seroma collection, or prolonged wound drainage [48]. On the other hand, poorly vascularized bulky subcutaneous fat tissue leads to lower oxygen tension in the peri-incisional zone, which is not favorable for wound healing [49]. Some studies have reported obesity as a risk factor for nasal carriage of *S. aureus* [28]. Also, innate immune response in the surgical field may be diminished in these patients, particularly in those with hyperglycemia [50, 51]. Prolonged surgical time due to intraoperative technical

challenges may increase the risk of PJI. Lastly, inadequate adjustment of prophylactic antibiotic dosing has also been mentioned as a potential cause for increased risk of PJI in obese patients [52]. These considerations provide ample explanation for the overwhelming evidence linking PJI and obesity [18, 53–56].

Smoking

Many smokers suffer from chronic obstructive pulmonary disease, atherosclerosis, and other systematic comorbidities that can confound the relationship between smoking and PJI. However, it has been demonstrated that smoking impedes the process of collagen synthesis and maturation in subcutaneous tissue surrounding surgical wounds [57].

It has also been demonstrated that smoking has a detrimental effect on bone healing following spinal fusion surgery [58]. Adequate oxygen supply is essential for tissue repair [59]. As well, wound hypoxia negatively affects neutrophil defense mechanisms against microorganisms and is a predisposing factor for infection [49]. Smoking can induce such hypoxia through different mechanisms. Nicotine releases catecholamines that lead to microvascular vasospasm and subcutaneous hypoperfusion. Nicotine also promotes platelet aggregation and formation of microthrombi. As well, inhaled carbon monoxide avidly binds hemoglobin to form carboxyhemoglobin, shifting the oxyhemoglobin dissociation curve to the left and significantly decreasing oxygen delivery to the peripheral tissues. Smoking cessation programs 6–8 weeks before elective hip or knee surgery have been effective in decreasing postoperative wound-related complications, especially infection [60, 61]. While detrimental effects of smoking on early postoperative complications seems to be evident, long-term studies on smokers who have undergone total hip or knee replacement have not found any significant association between smoking and PJI [54, 62].

Comorbidities

Patients undergoing joint arthroplasty commonly suffer from associated medical conditions [63, 64].

These conditions generally increase the risk of postoperative complications and negatively affect the final outcome of total joint arthroplasty [65–67]. They have also been related to higher mortality following total joint arthroplasty [8, 68].

Indices of Comorbidities

The number of comorbid conditions seems to have an independent cumulative effect on the risk of developing PJI [55]. Lai et al. demonstrated that the risk of PJI increased by 0.35 % for each additional patient comorbidity [69].

A number of methods to measure comorbidities have been described in the literature. The Charlson Index, initially created to predict 1-year mortality, has been validated for many different outcomes in various clinical conditions [70]. The Charlson Index is calculated utilizing a weighted set of comorbidities (Table 2.1) and age of the patient. Calculation is performed by summing the weighted comorbidities present and adding a point for each decade of life greater 40 years of age. Based on retrospective studies, it appears that progressive increase in Charlson Index

Table 2.1 Comorbidities included in the Charlson Comorbidity Index with their weighted scores

Weight	Disease
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
3	Lymphoma
	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Table 2.2 The three components of the NNIS System Surgical Patient Risk Index

American Society of Anesthesiologists Classification ≥ 3
Contaminated or dirty-infected wound
Surgery duration > 75th percentile of normal duration for surgery

greater than or equal to three significantly adds to the risk of infection [7, 71].

American Society of Anesthesiologists (ASA) physical status classification system is a nonspecific scoring to describe general health status before surgery, mainly by focusing on severity of comorbid conditions. It is utilized as an assessment tool for intra- and postoperative non-orthopedic complications. Although some studies have demonstrated a relationship between incidence of PJI and higher ASA scores [8, 56], others have found that the reliability and validity of the ASA score is questionable [72–74]. Moreover, ASA is principally based on severity rather than the type of comorbid conditions. Therefore, it is likely that the type of comorbidities might influence its predictive ability, rendering it less rewarding than other indices.

National Nosocomial Infections Surveillance (NNIS) System surgical patient risk index consists of three components (Table 2.2) [75]. The score ranges from zero to four, with one point assigned for each category. The 75th percentile for duration of arthroplasty has been listed as 2 h in previous reports, with some modifications suggesting a threshold of 1.5 h being appropriate [12, 76]. Some studies have indicated that NNIS index is a better predictor of SSI than its individual components and Berbari et al. observed a relationship between NNIS index and PJI [12, 75, 77, 78].

Specific Comorbidities Rheumatoid Arthritis

Approximately 5 % of patients undergoing total joint arthroplasty have rheumatoid arthritis (RA) [78]. In multiple studies, the risk of PJI in patients with RA has been shown to be higher than patients without [52, 79, 80].

The mechanism, however, that increases the PJI risk in RA patients remains unclear. A combination of the disease itself, their immunosuppressive therapeutic regimens, or other factors may be the cause [78]. These patients are inherently more susceptible to all infectious disorders, particularly those affecting bone, joint and soft tissues [81]. Also, patients with RA are at increased risk of early surgical wound complications such as superficial infection or dehiscence [82]. This can be explained to some extent by corticosteroid medications or other immune system modulators used in RA therapy [52, 83]. The medications that are employed to control RA have suppressive effect on immune system and affect negatively patients' defense against pathogenic bacteria. These medications include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic agents (DMARD) such as methotrexate, and recently developed biological agents such as tumor necrosis factor (TNF) antagonists or interleukin-1 (IL-1) antagonists.

S. aureus has been accounted as the most common pathogenic bacteria causing PJI in RA patients [84]. Interestingly, it has been shown that RA patients may be more likely to be colonized by *S. aureus* in their oropharynx and skin—possibly related to the combination of anti-TNF and methotrexate therapy [85, 86].

Methotrexate, a folate analogue, is the most common DMARD and has been considered the standard against which newer agents in the class are evaluated [87]. It inhibits neovascularization and decreases cytokine production. Although some studies had previously reported fewer complications with perioperative cessation of methotrexate in the RA population [88], prospective randomized studies in patients with methotrexate therapy who underwent elective orthopedic surgery (predominantly joint replacement surgeries) have not shown any increase in the risk of infection with continuation of methotrexate treatment within 1 year of surgery [89].

Cytokines are implicated in many aspects of pathogenesis of RA and modulation of their action alters the outcome of RA. Therefore, targeting these inflammatory mediators, especially

TNF, has been converted into a standard part of treatment in these patients [90]. It has been observed that anti-TNF therapy in RA patients who undergo total joint replacement increases the risk of PJI [91, 92]. A recent systematic review confirms that use of anti-TNF antibodies in the treatment of rheumatoid arthritis increases the risk of infections that require antimicrobial therapy and/or hospitalization [93].

Whether long-term methotrexate or anti-TNF therapy can be blamed for increased risk for PJI remains to be clarified, although recent reviews point out that higher doses of these medications did not impose a higher risk on these patients for severe infectious complications [94].

Lastly, being subjected to multiple joint replacements makes these patients more susceptible to hematogenous PJI during any episode of bacteremia. Furthermore, infection of one implant can predispose other implants to PJI although the risk of reinfection of the same implant is greater than a distant infection [79, 80, 95].

Hyperglycemia and Diabetes Mellitus

Based on the Nationwide Inpatient Sample (NIS) database, during the years 1988–2003, 8.5 % of patients who underwent primary or revision total joint replacement in the United States were diabetic [96]. Hyperglycemia with or without diabetes is a risk factor for suboptimal perioperative outcomes in patients undergoing orthopedic and non-orthopedic procedures. Clinical studies indicate that improvement in glycemic control lowers the rate of perioperative complications [97, 98].

Although little doubt exists regarding the role of diabetes and hyperglycemia as a risk factor for postoperative infectious and noninfectious complications in both diabetic and nondiabetic patients, it is less clear what parameter best delineates the riskiest situation for PJI among diabetics [51]. Some studies have reported patients with insulin-dependent diabetes are at greater risk of infection than non-insulin-dependent diabetics [99, 100]. Marchant et al. found that the odds of urinary tract infection (UTI) and cerebrovascular accidents were significantly higher in patients diagnosed with uncontrolled diabetes compared to controlled diabetics [101]. Soohoo et al. considered

complicated diabetics as those patients with any end-organ damage due to diabetes and found that both uncomplicated and complicated diabetes increased the risk of acute onset PJI after THA (1.7 and 3.7 times, respectively) [6].

The state of glycemic control appears to be another important aspect of infection prevention [23, 101, 102]. The link between hyperglycemia and the susceptibility to infection has been well-established [50]. The degree of consistent hyperglycemia correlates with impairment in various aspects of defense against bacteria, including vascular permeability, oxygen delivery and redox reactions, neutrophil adherence, chemotaxis, phagocytosis, efficacy of antibodies, function of complement components, and intracellular bactericidal activity. Furthermore, glucose can act as a pro-inflammatory mediator, stimulating cytokine production and inhibiting endothelial nitric oxide levels [51]. The preoperative serum glucose level at admission has been shown to be independent predictor of both morbidity and mortality in acute medical and surgical emergency settings [101]. Jämsen et al. demonstrated the link between preoperative outpatient hyperglycemia and PJI in TKA that remained significant even after adjustment for BMI [23]. Mraovic et al. reported that patients with PJI had significantly higher perioperative blood glucose values, including non-fasting preoperative and postoperative day one blood glucose levels [102]. They also observed that postoperative morning hyperglycemia greater than 200 mg per deciliter (mg/dL) doubled the risk of PJI. Moreover, nondiabetic patients were 3 times more likely to develop PJI, if their first postoperative morning blood glucose level was more than 140 mg/dL. Glycosylated hemoglobin or Hemoglobin A1c (HbA1c) level represents an average serum glucose concentration over the past 3-month period. Tight control of HbA1c has significantly decreased the occurrence and severity of many long-term complications of diabetes [103–105]. However, Iorio et al. did not observe any significant association between HbA1c levels and incidence of superficial or deep infections and concluded HbA1c is not a predictive marker for infection after TJA in diabetic patients [100].

Uncontrolled diabetes and hyperglycemia have been shown to be associated with an increased incidence of postoperative morbidity and mortality as well as increased length of hospital stay following lower extremity total joint arthroplasty [101, 102, 106–112]. The presence of diabetes raised the odds of developing PJI in both TKA and THA settings [55, 69, 99, 109, 110, 113]. In two retrospective investigations performed by Lai et al. and Iorio et al., diabetic patients had a fourfold increased risk for infection following total joint arthroplasty [69, 100]. The risks were stratified by Iorio et al. based on the procedure and were found to be much higher among hip procedures than among knee procedures [100]. This finding has not been confirmed by other studies [78].

Prolonged uncontrolled diabetes imposes a challenge to the surgeon, anesthesiologist, and other members of care-providing team [114]. Concomitant comorbidities such as obesity, metabolic syndrome, atherosclerosis, and hypertension along with already present multi-organ damage influence perioperative outcome of total joint replacement [115]. Furthermore, surgical wound healing is a concern among diabetic patients as hyperglycemia delays collagen synthesis. Wound-related complication rates following TKA have been reported between 1.2 % and 12 % in diabetic patients [108, 109, 111, 112].

Systemic Malignancy

Barbari et al. reported systemic malignancy not involving the index joint as a risk factor for PJI. They speculated that it was due to immunosuppressive effect of treatment for malignancy or unknown factors associated with the malignancy itself [78]. Bozic et al., however, observed that malignancy and metastatic tumor were not associated with an increased incidence of acute postoperative PJI [116]. Several case reports of hip and knee PJI due to uncommon pathogenic bacteria in the context of an underlying malignancy have been published [117–121]. These include PJI due to uncommon species of group D *Streptococcus* or *Clostridium* genera, *Klebsiella pneumoniae*, *Listeria monocytogenes*, and *Mycobacteria* and other microbes mainly associated

with colon, breast, ovarian and bladder cancers, as well as hematologic dyscrasia. While these associations suggest a sentinel role for uncommon microbes causing PJI (and a paraneoplastic role for PJI), they also demonstrate the exceptional vulnerability of the prosthetic host with baseline systemic cancer. Little evidence is available regarding the biologic mechanism. However, cancer and immune system dysfunction are in close relationship [122]. As many of these pathogens are traditionally intestinal, it is possible that weakened systemic and local defenses at the mucosal level, due to the cancer itself or anticancer therapy, were responsible for altered bacterial flora. Klein et al. demonstrated that patients with colon cancer had positive stool cultures for uncommon group D streptococci, significantly more commonly than matched controls [123]. These bacteria likely overcome the debilitated mucosal immune barriers and infect prosthetic material via hematogenous spread. As well, cases of PJI caused by *Mycobacterium bovis* have been described in patients who had previously been treated with intra-vesicular instillation of BCG vaccine (composed of *Mycobacterium bovis*) as immunotherapy for superficial bladder cancer [124].

Human Immunodeficiency Virus (HIV) Infection

The introduction of new antiretroviral regimens has led to a considerable improvement in both quality and life-expectancy of HIV-infected patients. As a consequence, an increase in the number of HIV patients presenting for total joint arthroplasty has been noted [52, 125]. An important subgroup of HIV-positive patients undergoing arthroplasty are hemophilic patients infected by contaminated factor concentrates in the past [126]. The main indications for arthroplasty in HIV/AIDS patients are osteonecrosis and hemophilic arthropathy, while simple osteoarthritis is not a common indication in this younger patient population [125, 127]. Hicks et al. found that the infection rate in HIV-positive hemophiliacs is greater than the general arthroplasty population—up to 18.7 % for primary surgery and 36.3 % in revision surgery during an average

follow up of 5.7 years [128]. Moreover, they observed that the risk of infection increased with time, and PJI-free survival at 1, 5, and 15 years was 95, 85, and 55 %, respectively.

HIV affects the immune system through depletion of CD 4+ lymphocytes. These leukocytes are mainly involved in cell-mediated immunity. However, other arms of the immune system are also indirectly affected [129]. During the course of the disease, disturbances in humoral immunity, monocyte-macrophage lineage, cytokine production, and polymorphonuclear function occur. These alterations, together with associated comorbidities such as malnutrition and intravenous drug abuse, predispose HIV-positive patients to common, as well as opportunistic, infectious complications [125, 129]. Moreover, due to the same mechanism of immune system malfunction, wound healing can also be influenced [129]. Furthermore, asymptomatic HIV-positive patients are twice as likely to be carriers of *S. aureus* [130]. Nevertheless, total joint replacement does not have any adverse effect on the rate of CD4+ reduction and progression to AIDS [131–133].

Common shortcomings of the studies regarding PJI in the context of HIV/AIDS seem to be small sample size, methodology issues, and confounding influence of hemophilia [52, 129]. While some authors believe the risk of late hematogenous infection increases with the deterioration in the immune system [129, 134], others are unable to confirm a link between lower CD4+ counts and the occurrence of surgical wound complications [125, 135, 136]. Others have proposed a viral load of over 10,000 copies per milliliter and symptomatic HIV-positive status as risk factors for SSI [52, 129]. The influence of HIV-positivity on the risk of late periprosthetic infection has been obscured by concomitant hemophilia in previous studies. There is no evidence to demonstrate whether HIV-positivity per se (and in the absence of other confounding risk factors such as intravenous drug use or hemophilia with frequent self-injections) increase the risk of late hematogenous PJI [129, 137, 138]. Unger et al.

presented midterm follow up of 26 TKA in 15 HIV-positive hemophiliacs (mean follow-up: 6.4 years; range: 1–9) without any case of PJI [132]. Some authors have suggested the risk of early and late PJI in HIV-positive non-hemophilic patients is probably higher than general population but lower than HIV-negative hemophilic patients, but this hypothesis is yet to be supported by evidence [126].

Sickle Cell Hemoglobinopathies

Advances in medical management of the patients with sickle cell hemoglobinopathies (SCH) have dramatically increased their life expectancy [139, 140]. This population undergoes total joint replacement usually at young age because of activity limitation and pain caused by osteonecrosis, most often in the hip and less commonly in the knee. Unfortunately, SCH patients present a unique set of challenges in terms of perioperative management and surgical technique [141, 142]. THA has been reported to have the highest rate of perioperative complications among orthopedic procedures performed for these patients [142]. Moreover, SCH patients are at greater risk for short-term and mid-term postoperative aseptic and septic complications [143]. Although earlier small case series reported an infection rate of up to 20 % following THA [144, 145], a recent report has demonstrated a much lower rate of 3 % that is still higher than general population [143]. Salmonella has classically been associated with bone infections in SCH. Yet, this microbe has not been reported as a cause of PJI in SCH, with *S. aureus* and gram-negative microbes being the most common pathogens [140, 142, 143]. Circumstances that can act as potential contributors to increased risk of PJI in SCH patients are coexistence of latent infection, osteonecrosis of the femoral head, increased intra- and postoperative blood loss due to bleeder hyperplastic bone marrow, increased surgical time due to surgical technical difficulties, and prolonged perioperative length of stay [141–143, 146]. Immunosuppressive effect of long-term treatment with hydroxyurea, the presence of stasis leg ulcers that exist in up to 20 % of SCH

patients, and hematogenous seeding following bacteremia that recurrently in this population can increase the risk of late hematogenous PJI [139–141]. The choice of cemented or cementless arthroplasty has been a matter of debate in SCH patients. Regarding PJI, some older studies suggested higher rate of infection with cemented THA [144, 145]. As well, a more recent case-series found only one case of PJI in 18 cementless THA [147]. Unfortunately, strong evidence directly comparing cemented versus uncemented arthroplasty in these patients is still lacking.

Hemophilia

Hemophilic patients may require arthroplasty at young age, due to debilitating end-stage chronic hemophilic arthropathy [148–150]. The prevalence of PJI in hemophilic patients has been reported from 1.4 to 16 % in recent studies [149–155]. Concerning for hemophilic arthroplasty patients, Galat et al. reported that patients with surgical site hematoma requiring early evacuation within 1 month of arthroplasty are more likely to suffer bleeding disorders and are at increased risk of PJI and major revision surgery [156]. Nevertheless, improvement of perioperative care has considerably decreased the occurrence of PJI [149]. Late PJI is now the main concern following TKA in hemophilic patients [151, 155]. Goddard et al. reported a 20-year survival rate of 97 % with infection as the endpoint, which is superior to the 10-year survival rate of 90 % and 77 % reported by Silva et al. and Zingg et al., respectively [149, 155, 157].

Complexity of TKA in these patients, due to anatomical challenges (severe arthrofibrosis, deformity, and bone stock deficiency), as well as high risk of surgical site hematoma and/or hemarthrosis may contribute to immediate postoperative risk of PJI [153, 155]. Immunosuppression associated with HIV/AIDS and Hepatitis C infection, and remote infections have been suggested as other predisposing factors for PJI in these patients [155].

Norian et al. reported *Staphylococcus epidermidis* to be the most common cause of PJI in these patients and concluded that hematogenous spread

during frequent intravenous self-administration of clotting factor concentrate is an important route of PJI in hemophilic patients [148].

Malnutrition

Optimal nutritional status is crucial for favorable surgical outcome. Malnutrition impedes collagen and proteoglycan synthesis and negatively affects wound remodeling. It also interferes with immune system function.

Several indices have been utilized for definition of malnutrition, the most common of which are serum albumin less than 3.5 g/dL, serum transferrin less than 200 mg/dL, and total lymphocyte count less than 1,500 per millimeter cubed [158, 159]. Other less common indicators of nutritional status are arm circumference and skin antigen-testing [158]. While these indices in general are good indicators of protein deficiency, they do not represent other aspects of malnutrition such as calorie and vitamin deficiency that can potentially be present in patients preparing to undergo total joint arthroplasty [160]. An increased rate of surgical wound complications has been observed in patients with perioperative nutritional depletion [159]. A post-surgical catabolic state follows any major surgery and is accompanied by loss of appetite and increased nutritional demand. Adequate nutritional reserve can lessen adverse effects of this physiologic response [161]. Malnutrition has been associated with increased surgical and anesthesia time, delayed wound healing, prolonged rehabilitation recovery, longer postoperative in-hospital stay, and increased hospital consults [159, 161–164]. Interestingly, malnutrition has been associated with failure of irrigation and debridement in the setting of persistent wound drainage following total joint replacement [165]. Various underlying conditions including aging can contribute to suboptimal nutritional status in malnourished patients. Whether malnutrition is an independent factor or it just represents patients' comorbid conditions has not been clearly addressed yet. Studies investigating long-term risk of PJI in nutritionally deficient patients are lacking.

History of Depression

In two separate analyses performed recently, Bozic et al. identified risk factors for PJI in the United States Medicare population [116, 166]. Notably, their analysis in TKA cases found that depression was an independent predictor of subsequent PJI [166]. The pathophysiology of this relationship is unknown and unconfirmed by other studies. However, Bozic et al. did hypothesize that the physiologic depression may be associated with malnutrition leading to the increased risk of PJI. Interestingly, Bozic et al. also identified psychoses as independent predictor of PJI following both THA and TKA [116, 166].

Posttraumatic Arthritis

Patients who undergo total hip replacement because of posttraumatic osteoarthritis have been demonstrated to be at higher risk for PJI in comparison with those with arthroplasty due to primary osteoarthritis [20]. Potential explanations for this include the complexity of the procedure, prolonged surgical time, and less favorable status of soft tissue.

Moreover, secondary total hip replacement due to hip fracture has also been shown to be an independent risk factor for PJI [8, 20]. The reason for this finding is unknown, but systemic reactions to trauma as well as local tissue injury at the site of arthroplasty may predispose these patients to infection. Other possible factors are unfavorable underlying health status of the patient suffering hip fracture and lack of adequate preoperative conditioning (such as optimal control of comorbid conditions or associated infections).

Similar to hips, previous knee trauma requiring open reduction and osteosynthesis, particularly with the remnants of internal fixation material at the time of arthroplasty has been reported as a risk factor for PJI [9, 167]. However, arthroscopy and high tibia osteotomy did not increase the risk of PJI [167]. The vulnerability of patients who undergo TKA for posttraumatic osteoarthritis is particularly important since these patients are often younger than the typical population requiring arthroplasty.

Medications

Non-steroidal Anti-inflammatory Drugs

NSAIDs exert their analgesic and anti-inflammatory effect through two different mechanisms: inhibition of prostaglandin (especially prostacyclin) and thromboxane synthesis by cyclooxygenase enzymes (COX-1 and COX-2) and also by interference with protein–protein signals that lead to white blood cell activation [168]. These agents play a crucial role in the multimodal perioperative pain management for total joint arthroplasty [136]. Some concerns have been expressed for the use of NSAIDs in this setting, mainly because of their adverse effect on platelet aggregation and subsequently increased risk of bleeding [52]. These drugs have a variable effect on hemostasis as far as bleeding risk is concerned [170]. While Robinson et al. demonstrated increased risk of excessive blood loss with the use of NSAIDs [171], analysis of more recent data does not show a significant increase for bleeding risk or transfusion requirement with NSAIDs or selective COX-2 inhibitors [169]. Regardless, direct evidence linking the use of NSAIDs with increased risk of PJI does not exist. In the study reported by Pederson et al. based on Danish arthroplasty registry, incidence of PJI among patients who received postoperative NSAIDs as prophylaxis for heterotopic ossification was the same as those who did not receive it [11].

Platelet Function Inhibitors

Clopidogrel inhibits platelet aggregation by binding to adenosine deaminase G-protein-coupled receptor on the platelet surface. Due to its irreversible binding, the effect of Clopidogrel will persist for the remainder of the platelet's existence, approximately 1 week. Similarly, low-dose aspirin permanently inhibits platelet activation by blocking thromboxane-dependent pathways [172].

Unfortunately, little evidence exists regarding the impact of antiplatelet medications in patients undergoing arthroplasty and most of the studies have been performed in the field of coronary artery bypass surgery.

Platelet function inhibition can cause excessive bleeding, leading to considerable blood loss and requirement for blood transfusion and surgical site complications such as prolonged drainage, hematoma formation, or infection [173, 174]. Furthermore, the risk of infection at the surgical site appears to be greater if the patients are under dual antiplatelet therapy (aspirin plus Clopidogrel) preoperatively [173].

Basic science studies also suggest a role for platelets in the innate and adaptive immune system. Platelets contribute to recruitment of leukocytes to the site of vascular injury, release cytokines that augment the immune response, liberate some antibacterial proteins, and expand antibody production through their interaction with lymphocytes [175, 176]. However, the clinical consequence of platelet function blockade on the immune system has not been precisely investigated. In a retrospective study, Nandi et al. found that discontinuation of Clopidogrel 5 days before elective hip and knee arthroplasty was associated with a lower rate of reoperation and antibiotic use for infection, wound cellulitis, and wound drainage [177]. They also observed that the timing of Clopidogrel resumption following arthroplasty did not affect the rate of postoperative events. Another finding of this study was the unexpectedly higher rate of infection (6 %) among patients taking Clopidogrel, which could be due to multiple other factors, but underscores consideration of these patients as high risk for PJI.

Anticoagulants

Anticoagulation is a routine component of perioperative management of arthroplasty patients in order to reduce the risk of postoperative thromboembolic complications [178, 179]. A wise balance should exist between efforts to prevent thromboembolism and the potential risk of bleeding complications [180]. However, evidence shows that hemorrhagic complications are not the sole concern with prophylactic anticoagulation therapy. Blood collections (hematomas) usually resorb without any associated adverse event, but when large enough, they can lead to surgical wound problems such as skin necrosis and persistent wound drainage [181, 182]. Galat et al.

observed hematomas that required evacuation within 1 month of TKA were associated with significantly increased risk of PJI with 2-year cumulative probability of 10.8 % in comparison with 0.8 % in patients without hematomas [156].

Higher rates of clinically important hemorrhagic complications have been reported among patients taking injectable forms of low molecular weight heparin compared to oral warfarin [182, 183]. One study comparing patients who received warfarin as preoperative thromboprophylaxis for total joint arthroplasty with those who did not receive any form of thromboprophylaxis, reported that prophylactic warfarin was associated with greater likelihood of both superficial and deep surgical wound infections [184]. Furthermore, Minnema et al. and Parvizi and et al. found that international normalized ratio (INR) greater than three is significantly associated with wound-related complications (such as bleeding, hematoma formation, persistent drainage) as well as deep PJI [180, 185]. These findings suggest a relationship between the degree of anticoagulation and the risk of PJI that may negate the beneficial effects of anticoagulation.

Previous Operation in the Same Joint

Several retrospective studies have indicated previous operation at the site of arthroplasty is a risk factor for PJI for both hip and knee joints [55, 78, 186, 187]. It has been hypothesized that scar tissue formation due to prior surgical procedures can result in longer surgical time [55]. Moreover, poorly planned skin incisions, and devitalized peri-incisional tissues can also contribute to surgical wound complications [186].

Staphylococcus Aureus Colonizers

Nasal carriage of *S. aureus* was identified as a risk factor for SSI several decades ago. External nares are the most consistent area in the body from which *S. aureus* can be isolated [188]. Colonization occurs through interaction of staphylococcal surface proteins and mucin carbohydrates on the

surface of the epithelial cells [189]. Recent technology has made it possible to detect nasal *S. aureus* carriage within hours [190]. Elimination of nasal carriage by topical nasal antibiotic has led to disappearance of *S. aureus* from other parts of the body. Moreover, correlation between the colonization density of *S. aureus* at the carriage site and the risk of infection reinforced the theory of this causal relationship [188]. In a prospective study, Kalmeijer et al. demonstrated that nasal carriage was the single independent risk factor for the development of *S. aureus* SSI [24]. The general population can be divided into three groups according to the pattern of carriage: persistent carriers (20 %), intermittent carriers (60 %), and noncarriers (20 %). Current carriage of *S. aureus* in the general population has been reported to be 37.2 % [188]. A diverse set of factors including demographic, genetic, immunologic, hormonal, and healthcare-related, along with bacterial antigenic factors have shown to influence the staphylococcal nasal carriage state. In patients with staphylococcal SSI, indistinguishable strains of *S. aureus* have been isolated from the surgical site and nares of 80 % of patients [191]. Moreover, colonizing strains may spread to other patients.

The most recent Cochrane analysis of surgical trials studying the effect of preoperative nasal mupirocin application in *S. aureus* carriers to decolonize the patient demonstrated a significant reduction in the rate of nosocomial *S. aureus* infection rate. However, when SSI was analyzed as the primary outcome, no statistically significant difference was found [192]. Interestingly, analysis of the infection rate caused by microorganisms other than *S. aureus* demonstrated slightly higher (Relative Risk=1.38) but statistically significant risk of infectious complications in mupirocin group. This may indicate a risk of *S. aureus* being replaced by other microbes in patients who receive nasal mupirocin. Other studies, however, have shown that eradication of *S. aureus* before surgery appears to lower SSI rates due to *S. aureus* [193, 194]. While a clear link appears between nasal carriage of *S. aureus* and SSI, its association with deep infection and the effect of decolonization require further research for clarification.

Surgical-Related Risk Factors

Surgeon and Hospital Volume

The incidence of postoperative complications, including PJI, following joint arthroplasty has been shown to be related to both the surgeon's and hospital's arthroplasty volume [1, 195–198]. These findings hold after adjusting for potential confounders that may have been associated with volume, such as patient age, gender, and overall health. This association may be explained by the link between increased surgeon volume and decreased operative time, an indication of improved operative technique, decreasing the risk of contamination [16, 55, 56, 199, 200]. As well, Bozic et al. described a relationship between increased surgeon volume and decreased hospital length-of-stay [195], likely resulting in decreased exposure to nosocomial organisms [56]. Similarly, increased hospital arthroplasty volume has been associated with decreased length-of-stay [56, 201]. It could be expected that the healthcare team at a high-volume institution is more familiar with the early signs and risks of developing infection and therefore is more able and quick in implementing preventative care to mitigate PJI. Katz et al. studied the relationship between decreasing rates of PJI with increasing arthroplasty volume for both knees and hips [1, 196]. In these analyses the risk of PJI decreased by approximately half for surgeons and hospitals performing greater than 50 and 100 arthroplasties per year, respectively. While this trend ($p < 0.1$) did not achieve statistical significance, it is a concerning finding that highlights the importance of experience in minimizing postoperative complications, especially PJI.

Joint

Prosthetic hips and knees may not be in equal jeopardy of infection. Kurtz using National Inpatient Sample database between years 1990 and 2004 observed that the incidence of PJI in both knees and hips were similarly progressively increasing, with the incidence doubling

for both joints at the end of the same time period. However, the burden of PJI following TKA was consistently greater than following THA [5]. Pulido et al. also indicated TKA as a risk factor for PJI (hazard ratio of 2.85) [56]. Other studies have reported more infections occur after tricompartmental than unicompartmental knee replacement, rising to a threefold difference in PJI incidence after 10 years of follow-up [10, 19, 202, 203].

Revision Arthroplasty

Revision arthroplasty has consistently been reported to be at higher risk of infection in comparison to primary arthroplasty [2, 9, 78, 113]. Poss et al. reported that revision arthroplasty was 8 times more likely to be infected [204]. Jämsen et al. reported mean hazard ratios of 3.4 and 4.7 for partial and total knee revision, respectively, based on registry analysis with a median follow up of 3 years [9]. Blom et al. observed that introduction of strategies such as strict use of prophylactic antibiotic regimens, antiseptic solutions, occlusive clothing, and vertical laminar flow in operating rooms considerably reduced the incidence of PJI following primary and revision TKA from 4.4 % and 15 % to 1 % and 5.8 %, respectively [205]. However, they found revision procedures to be at significantly higher risk of PJI. Moreover, Ahnfeldt et al. confirmed that higher numbers of previous revision procedures have been associated with greater risk of PJI [206]. Prolonged operating time, comorbidities, increased need for blood transfusion, and higher incidence of postoperative wound complications could confound the association between revision surgeries and PJI, but even after accounting for these variables, the link between revision arthroplasty and PJI remained [78].

Operative Time

Operative time—the duration from skin incision to completion of closure—has been linked to PJI as an independent parameter and also as a component of NNIS index [8, 78, 200, 207, 208].

Berbari et al. defined a long arthroplasty procedure as one taking greater than 3 h [78]. When incorporating this definition into the NNIS surgical patient risk index score (a composite of surgical and patient factors), they found a significant independent association between this index and subsequent PJI. Similarly, Leong et al. defined an prolonged THA or TKA as greater than 2 h [208]. In their analysis, the incidence of SSI was significantly higher for prolonged procedures [208].

Ridgeway et al. studied primary and revision THA separately and found a significant increase in the incidence of SSI for interventions that lasted more than 2 h in comparison with those lasting between 60 and 89 min [8]. However, they did not observe any significant association between the procedure time and PJI in hip hemiarthroplasty. The same observation was reported by Leong et al [208]. Since the incidence of PJI in hip hemiarthroplasty was nearly twice of THA in both studies, this may indicate that the presence of other risk factors in patients undergoing hip hemiarthroplasty (particularly patient-related factors such as age, comorbidities, and baseline level of activity) may have obscured the effect of procedure duration on incidence of PJI.

Although prolonged operative time can be considered a measure of duration of exposure to potential contaminants, it can also reflect complexity and technical aspects of the procedure as well as the degree of tissue damage during the surgery [8, 208]. While procedure duration is an intuitive and well-proven indicator of PJI risk, the evolution of surgical techniques for arthroplasty has likely led to shorter procedure times with different techniques and therefore these arbitrary thresholds of duration may have varying efficacy in predicting PJI.

Previous Procedure in Operating Room

A common sense practice in orthopedic surgery, and especially in arthroplasty, is organizing the operating room (OR) such that confirmed or suspicious cases of infection are performed at the end of the OR session minimizing the risk to

uninfected procedures. Whether the practice of performing the so-called clean arthroplasty procedure following an infected case increases the probability of infection has not been adequately studied. The only evidence is a retrospective study in which 39 “clean” total joint replacement procedures were performed after a confirmed infection-related intervention. Of these, only one case developed PJI within 9 weeks of surgery with the same pathogenic bacteria as encountered in the preceding infectious case [209]. Despite lacking definitive evidence of cross-contamination, the theoretical risk exists and should be considered.

Anesthetic Management

Although the influential role of anesthesia processes during the surgical intervention for immediate perioperative outcomes is well-known, up until recent years less attention has been devoted toward long-term consequences of intraoperative anesthetic management [210]. Modern anesthetic process utilizes short acting medications and the operative time and consequently anesthesia time are shortening. Nonetheless, some aspects of anesthetic management can improve host defense against contamination during surgery and therefore are considerable prophylactic measures against SSI [211]. These practices are: maintaining physiologic normothermia, providing supplemental oxygen, retaining euvoletic state, adequate peripheral tissue perfusion, optimal management of hyperglycemia, timely administration of antibiotics, and judicious use of blood transfusion in the perioperative period [210, 211]. Intraoperative hypothermia is thought to increase the risk of SSI through vasoconstriction and reduction of oxygen supply in the subcutaneous tissue. Adequate perfusion and oxygen tension at the surgical site are mandatory for optimal function of different arms of the immune system, as well as wound healing process [212]. Short-term hyperglycemia has detrimental influence on body defense against microbes in the surgical field [213]. Nonenzymatic glycosylation deactivates antibodies and blocks C3 complement component. Hyperglycemia also

impairs chemotactic, bactericidal, and phagocytic performance of the neutrophils [211, 213].

Although some retrospective studies, designed for investigation of risk factors for adverse outcomes of total joint replacement were unable to find any statistically significant difference between types of anesthesia and PJI [11, 214], one retrospective population-based study focusing specifically on the relationship between type of anesthesia and SSI in arthroplasty found that total hip and knee arthroplasty under general anesthesia are associated with higher risk of SSI compared with neuraxial (epidural or spinal) anesthesia. The odds ratio of SSI after adjusting for type of surgery, age, sex, comorbidities, year of surgery, surgeon’s age, and teaching status of the hospital was found to be 2.21 for general anesthesia compared to neuraxial [215]. This finding has been explained by different mechanisms. First, the peripheral vasoconstriction induced by surgical stress is probably more pronounced in general anesthesia, since this type of anesthesia unlike neuraxial anesthesia does not block the sympathetic autonomic system. This can lead to lower perfusion and oxygen tension at the site of surgical wound. Second, volatile anesthetics and opioids can negatively affect various types of cells involved in the immune response. Lastly, neuraxial anesthesia provides postoperative analgesia that prevents pain-induced generalized vasoconstriction and diminished peripheral perfusion [215, 216].

Postoperative Risk Factors

Prior to Discharge

Persistent Postoperative Wound Drainage

Persistent postoperative wound drainage has been shown to be associated with deep infection after total joint arthroplasty [180, 217]. A clear definition for persistent postoperative wound drainage does not exist. Generally it is accepted that wounds that continue to drain more than 48 h postoperatively should be cautiously monitored [165]. It has been proposed that if the surgical

wound continues to drain more than 5–7 days, it is 12.5 times more likely to develop infection and often the drainage is prolonged [217, 218]. Evidence shows with every additional day of prolonged drainage, the probability for infection is substantially increased by 42 % in hips and 29 % in knees [48]. Moreover, prolonged drainage extends the hospital stay [48].

Risk factors associated with prolonged wound drainage are numerous. Higher volume of drain output is an independent factor [48]. Conditions that intervene with wound healing (i.e., diabetes mellitus, rheumatoid arthritis, malnutrition, immune modifying medications, smoking, advanced age, and obesity) can potentially predispose the patients to worrisome wound drainage [219]. Postoperative antithrombotic prophylaxis with low molecular weight heparin has been associated with longer drainage in comparison with aspirin and warfarin [48]. Persistent postoperative wound drainage clearly increases the risk of PJI. However, a clear delineation between prolonged drainage and the inevitable development of PJI has yet to be determined, complicating management.

Surgical Wound-Related Complications

Although surgical wound-related complications such as dehiscence, skin-edge necrosis, superficial infection, and delayed healing rarely require surgical intervention, it has been shown that they are associated with deep wound infection and increase the risk of PJI up to 4 times within 5 years after total knee replacement [81]. Therefore, patients with successful treatment of SSI should be closely monitored for any possibility of deep PJI in the future [217]. As discussed below, any tactic that decreases the incidence of SSI confers significant benefit for the prevention of PJI.

Distant Infection

The presence of infection distant to the prosthetic joint can be an initiating event in the development of PJI. Through hematogenous spread, organisms incubating at a distant site can be introduced to the prosthetic joint, which can provide an optimal site for growth. Common infections in the hospital setting that have been shown

to predispose to PJI include UTI, pneumonia, bacteremia, and SSI [9, 56, 78, 185, 220–222]. Pulido et al., in a case–control series, found that postoperative UTI independently increased the risk of PJI by over fivefold [56]. This relationship has been supported by other investigations [78, 113, 185]. In an analysis of Gram-negative PJI, Zmistowski et al. found PJI had developed secondary to UTI in 13 % of those patients with Gram-negative PJI compared to 0.4 % in Gram-positive PJI [222]. Use of an indwelling urinary catheterization is a known risk factor for UTI [223, 224]. Indwelling catheter use, however, has been promoted in anesthetized patients during joint arthroplasty due to concern regarding urinary retention [225, 226]. Interestingly, Iorio et al. found a significant relationship between the development of UTI and the use of indwelling catheterization versus straight catheterization [223]. This is contrasted with Hozack et al., who found no benefit of straight catheterization over indwelling catheterization in the perioperative setting [227]. In patients receiving indwelling catheters, the risk of UTI development, and hypothetically the risk of PJI, is proportional to the duration of catheterization [224]. The management of urinary retention and patients presenting with asymptomatic UTI in the perioperative arthroplasty setting remains controversial. Regardless, the theoretical risk of seeding a prosthetic joint leading to PJI from the urinary tract has been observed on numerous occasions justifying concern for joint integrity when presented with UTI.

The development of nosocomial pneumonia during a hospital stay is not an uncommon event [228–230]. However, pneumonia complicating the postoperative course of joint arthroplasty is a much less common event. In two separate analyses, Parvizi et al. and Pulido et al. found a 0.1–0.15 % incidence of in-hospital pneumonia following total joint arthroplasty [231, 232]. As well, Mahomed et al. found that 1.4 % of patients developed pneumonia within 90 days of knee arthroplasty [2]. The development of pneumonia provides another opportunity for pathogen (notably *Streptococcus pneumoniae*) exposure to the prosthetic joint. In their case–control analysis,

Berbari et al. found that patients suffering PJI were over twice as likely to have a history of nosocomial infection, including pneumonia, compared to the uninfected controls [78]. This finding was not statistically significant ($p < 0.1$) and did not survive multivariate analysis; however, this could be argued to be a type-two error due to the low incidence of nosocomial infections in post-arthroplasty patients. Puldio et al. also investigated the possibility of a relationship between postoperative pneumonia and PJI, with no significant findings [56]. Interestingly, Katz et al. found that both surgeons and hospitals with high annual knee arthroplasty volumes had significantly lower rates of postoperative pneumonia development [1].

The development of bacteremia in the hospital can occur secondary to many diseases, some of these already discussed. However, another route of entry is via venous catheters, which provide pathogens a direct route of entry into the blood stream [233]. Following joint arthroplasty, the development of documented bacteremia is uncommon [232]. Yet, bacteremia, specifically *Staphylococcus aureus* bacteremia (SAB), has been associated with the development of PJI [220, 221, 234]. Murdoch et al. found an incidence of PJI development through hematologic seeding of the joint in 34 % of patients who presented with concomitant prosthetic joint and SAB [220]. Similarly, Sendi et al. found that 39 % of patients presenting with SAB and in situ prosthetic joint developed PJI [221]. It is worth noting, however, that in attempts to isolate only cases with PJI secondary to bacteremia (not cases of bacteremia secondary to PJI), Sendi et al. and Murdoch et al. limited their definition of hematogenous spreading to those cases that occurred at a minimum of 1-year postimplantation. Therefore, the relationship between bacteremia in the acute postoperative hospital setting and PJI remains unknown. However, it has been found that hospital-acquired SAB carries a lower risk of subsequent PJI than community-acquired SAB [221, 234].

Postoperative pathogen introduction into the joint during the hospital stay that does not require the traditional hematogenous seeding is

superficial SSI. The association between SSI and the development of deep infection is well established [78, 113, 217]. In the acute setting there exists minimal barrier between the superficial compartments and the joint space. Of course this ease of passage provides ambiguity in the temporal relationship between deep PJI and SSI. In their case-control study Berbari et al. observed an adjusted odds ratio of nearly 36 for an association between SSI and PJI [78]. These findings exhibit the strong relationship between SSI and PJI. Factors leading to poor wound closure or introduction of pathogens into the superficial space predisposes to SSI and therefore PJI. One such factor is postoperative hematoma formation. It is evident and expected that infectious events occurring regional to the joint strongly predispose to PJI.

Cardiovascular Complications

As a primary transporter in immunologic response, required nutrients for timely wound closure, and potential pathogens, the cardiovascular system plays an important role in the development of PJI. Specific diseases that have been known to facilitate PJI are postoperative atrial fibrillation and myocardial infarction. Pulido et al. reported that atrial fibrillation and myocardial infarction had odds ratios of 6.2 and 20.4, respectively, as independent predictors of PJI [56]. The authors hypothesized that these findings were associated with subsequent anticoagulation and association with overall poor health and therefore led to the development of PJI. Subsequently, Bozic et al. utilized a large national database to isolate congestive heart failure, peripheral vascular disease, and valvular disease as cardiovascular diseases predisposing to PJI [116, 166]. The pathophysiology leading from cardiovascular disease to PJI remains unknown, yet the relationship is established and many potential mechanisms can be described. These include increased use of anticoagulation, deprivation of essential nutrients and hypoxia, and effects from thromboembolic events.

Allogenic Blood Transfusion

The use of blood products in the postoperative setting is an essential management tool for

postoperative anemia, and in many ways aids in the prevention of PJI [56, 116]. However, when autologous blood products are not available or depleted, the use of allogeneic blood becomes necessary. Such use has been associated with PJI [56, 78, 180, 235]. Transfusion of allogeneic blood has a known immunomodulating response, which may be the cause for increased risk of PJI [236]. However, Parvizi et al. hypothesized that allogeneic transfusions are simply a proxy for increased blood loss, hematoma formation, and wound drainage—the true causes of PJI [180].

Length of Stay

As has been previously discussed, increased duration of hospital stay provides increased risk for establishment of PJI. Exposure to nosocomial pathogens, including those already mentioned, suggests caution in increasing hospital length of stay. Such nosocomial infections include the development of pneumonia, UTI, and bacteremia. An increased length-of-stay may also indicate a poor postoperative course with noninfectious complications increasing the risk of joint contamination. Cardiac, pulmonary, or wound complications would create such a scenario. Appropriate length-of-stay remains a contentious issue in the arthroplasty community with conflicting reports. On the one hand, it is argued that the shift to shorter hospital stay has led to increased rates of preventable readmissions [64]. While on the other hand, evidence has been provided that earlier discharge of a stable patient has no effect on rates of readmission [237, 238]. From the perspective of PJI, it is logical that removal from the hospital setting would lessen the risk of contamination. This logic is supported by the association between high-volume arthroplasty centers and decreased length-of-stay with concordant decreased rate of PJI [1, 195, 196]. The appropriate length-of-hospital-stay remains unproven, yet it is accepted that importance exists in minimizing the risk of PJI by decreasing the duration to the shortest length without compromising the health of the individual. This appropriate duration is likely dependent upon the individual, surgeon, and hospital and not constant throughout the joint replacement community.

Post-discharge

Dental Work

Another potential nidus for infection is dental compromise. In this case, normal dental flora can cause transient bacteremia. The normal flora is most often not pathogenic. However, the theoretical risk for the development of PJI in the setting of poor dental hygiene or following dental procedures has led many surgeons and organizations to adopt prophylactic guidelines including the use of pre-arthroplasty dental clearance and post-arthroplasty antimicrobial prophylaxis prior to dental procedures. The necessity of these guidelines is controversial due to the lack of strong evidence supporting them [239–243]. Berbari et al. performed a case–control study investigating an association between post-arthroplasty dental work and PJI with no association identified [244]. However, anecdotal evidence provided by case reports and series do suggest that bacteremia with a dental source can lead to PJI [245–248]. While the theoretical risk of hematogenous prosthetic seeding does exist, it has been argued that the volume of bacteria introduced into the bloodstream is insufficient for creation of PJI [239]. Furthermore, with the relatively low incidence of PJI, it has not yet been possible to accurately determine the risk of subsequent dental procedures for the development of PJI, or more importantly the protective effect of antibiotic prophylaxis prior to such procedures.

Subsequent Surgery

As often discussed in this chapter, anything providing a risk of bacteremia provides a risk of PJI. Invasive surgery, including subsequent arthroplasty on another joint or revision surgery provides such a risk. As well, the risk of PJI developing in prosthetic joints when distant to an infected joint has been investigated [95]. Jafari et al. studied 55 cases in which a patient suffering PJI had another prosthetic joint, finding that 11 cases (20 %) developed PJI in the distant joint. However, it is unknown if this increased risk exists due to seeding from the infected joint or because these patients are predisposed to infection secondary to other risk factors. The later theory is supported by the

finding that only four cases (7.2 %) were infected by the same pathogen in both joints.

Similarly, when providing patients relief from multiple degenerated joints, arthroplasty as staged or simultaneous procedures must be considered. When patients require bilateral arthroplasty, simultaneous arthroplasty appears to be protective against PJI over staged bilateral arthroplasty [249–251]. However, other complications—thrombolytic, cardiac, and overall mortality—have been shown to be increased in simultaneous compared to staged bilateral procedures [252]. Regardless of the timing, multiple surgical procedures around or following arthroplasty, does provide an increased risk for PJI and the influence of any other present factors will influence the outcome.

Long-Term Stay in Healthcare Facility

Length of hospital stay has been shown to be a risk factor for PJI likely both as a marker of decreased health status and increased exposure to nosocomial pathogens. The same logic could be applied to the discharge to long-term healthcare facilities and increased length of stay at such facilities rather than a discharge home. The evidence to support this logic, however, is lacking. Discharge disposition following arthroplasty has been contentious recently for its potential effect on hospital readmission rates. Due to the aforementioned reasons, it is likely to be found predictive of subsequent PJI as well. Eliminating the events leading to prolonged hospitalization and discharge to a long-term care facility is likely to lower the risk of PJI.

Conclusion

Many factors are associated with the development of PJI. They include patient, institutional, surgical, and postoperative care factors. Patient selection, or rather optimization, prior to elective arthroplasty is imperative in lowering the risk of a devastating complication that can lead to systemic injury. Unfortunately, the evidence on correction of host disease and the effect on risk of PJI is limited. However, it is well established that

patients with significant comorbidities are at great risk for PJI and should be counseled as such. Institutional and surgical teams should also be well-informed of practices—such as early treatment of wound discharge, decreased operative times, and improved anesthesia—that can limit the risk of PJI. No arthroplasty patient is ever PJI risk-free; however, knowledge of these established risk factors and appropriate patient care may help to mitigate such risks.

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