Review Article

Patient-related medical risk factors for periprosthetic joint infection of the hip and knee

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Abstract: Despite advancements and improvements in methods for preventing infection, periprosthetic joint infection (PJI) is a significant complication following total joint arthroplasty (TJA). Prevention is the most important strategy to deal with this disabling complication, and prevention should begin with identifying patient-related risk factors. Medical risk factors, such as morbid obesity, malnutrition, hyperglycemia, uncontrolled diabetes mellitus, rheumatoid arthritis (RA), preoperative anemia, cardiovascular disorders, chronic renal failure, smoking, alcohol abuse and depression, should be evaluated and optimized prior to surgery. Treating patients to get laboratory values under a specified threshold or cessation of certain modifiable risk factors can decrease the risk of PJI. Although significant advances have been made in past decades to identify these risk factors, there remains some uncertainty regarding the risk factors predisposing TJA patients to PJI. Through a review of the current literature, this paper aims to comprehensively evaluate and provide a better understanding of known medical risk factors for PJI after TJA.

Keywords: Total joint arthroplasty (TJA); periprosthetic joint infection (PJA); prevention; risk factors; preoperative optimization

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Introduction

Total joint arthroplasty (TJA) is a surgical procedure that provides pain relief and restores function for patients suffering from debilitating arthritis (1). The number of TJAs performed annually has risen in recent years and is expected to reach 572,000 for total hip arthroplasty (THA) and 3.48 million for total knee arthroplasty (TKA) by 2030 (2,3). Despite the overall success of the procedure, periprosthetic joint infection (PJI) is a rare but devastating complication that is a major cause of failure after TJA (4,5). As the number of TJAs increases with time, the number of PJIs is also expected to increase, leaving more patients with the burden of compromised function and reduced quality of life (1). Despite established perioperative methods of preventing infection, there are multiple medical risk factors that predispose patients to infection.

Medical conditions, such as obesity, diabetes and rheumatologic disease, have been reported as consistent risk factors for PJI (5-7). However, a great deal of variability exists in the literature with regards to other medical conditions that have been reported as risk factors for infection, including coagulopathy, preoperative anemia, congestive heart failure, chronic pulmonary disease, depression, renal disease, pulmonary circulation disorders, psychoses, metastatic tumor, peripheral vascular disease, and valvular disease (7-11). Strategies to reduce the rate of PJI in TJA patients should begin with addressing these modifiable, patient-related, medical risk factors. It is imperative that orthopaedic surgeons understand and identify these risk factors prior to TJA so that they can develop interventions to optimize patients and minimize their risk of developing a postoperative infection. Therefore, the purpose of this review is to describe the risk factors associated with PJI and current strategies for preventing infection.

Morbid obesity

Obesity is a major health concern in the United States, as being obese is associated with increased risk for other comorbid conditions, such as diabetes mellitus, ischemic heart disease, hypertension, poor nutritional status and early mortality (12). Obese patients are more likely to undergo TJA (12), but these patients have a higher incidence of perioperative complications (10,13-15). Obese patients have an increased risk of PJI after THA [adjusted hazard ratio (HR) =1.73] and after TKA (HR =1.22) (5,8). The risk of PJI has been shown to increase exponentially with body mass index (BMI), as BMI >40 kg/m^2 (obese) increased the risk of infection by 3.3 times, while a BMI >50 kg/m^2 (morbidly obese) increased the risk of infection by 21 times (15,16). Likewise, Jämsen *et al.* evaluated 7,181 primary TJAs and reported that the infection rate increased from 0.37% in patients with normal BMI to 4.66% in morbidly obese patients (17). Thus, morbid obesity has frequently been implicated as an independent risk factor for PJI in several studies.

Obese patients may be at increased risk of PJI due to prolonged operative time, increased need for allogeneic blood transfusion, and the presence of other medical comorbidities (18-20). This patient population is also at an increased risk of wound dehiscence due to increased surface tension at the surgical site, as well as postoperative surgical wound complications such has hematoma formation and prolonged wound drainage that may increase the risk of PJI (21,22). Obese patients undergoing TJA are also at increased risk of developing an infection due to "paradoxical malnutrition", as these patients are often malnourished despite their obesity (5). Interestingly, studies have shown that the effects of obesity on the risk of PJI decline with time. Bozic *et al.* reported that the risk of PJI associated with obesity was 19% lower (P=0.025) 1 year after TJA (7).

Preoperative weight reduction should be recommended to minimize the risk of PJI in morbidly obese patients undergoing elective TJA (5). While an absolute cutoff with respect to BMI has yet to be established, orthopaedic surgeons should attempt to optimize obese and morbidly obese patients to BMI below 40 kg/m^2 preoperatively while maintaining overall nutritional status (23).

Malnutrition

While several underlying conditions, such as age and obesity, can potentially contribute to the poor nutritional state in malnourished patients, malnutrition independently increases the risk of PJI in patients undergoing TJA (5,22,24,25). Malnutrition can be defined as a serum albumin level <3.5 g/dL, serum transferrin levels <200 mg/dL, serum prealbumin <15 gm/dL and total lymphocyte count (TLC) <1,500 cells/mm^3 (22,26). Green *et al.* reviewed the records of 217 patients undergoing primary TJA and found that there was 5 times greater risk of PJI in patients with preoperative TLC <1,500 cells/mm^3 and a 7 times greater risk of infection in patients with albumin levels <3.5 g/dL (25). For revision TJA, Yi *et al.* prospectively evaluated 600 patients and reported a high infection rate of 7% in patients that had one or more parameters positive for malnutrition compared to 1% in patients without malnutrition (P=0.003) (27). Malnutrition has been shown to interfere with optimal synthesis of collagen and proteoglycan, resulting in disruptions in the wound healing process that can lead to persistent wound drainage and increased risk of infection (22,28,29).

The current definitions of malnutrition are effective for identifying protein deficiency, however, they fail to indicate other aspects of malnutrition including caloric or vitamin deficiency (22,30). For example, Maier *et al.* reported a higher prevalence of vitamin D deficiency in PJI patients compared to non-infected patients (4). This indicates a need for more comprehensive parameters for defining malnutrition and also suggests a need for screening and treating hypovitaminosis D before orthopaedic surgery.

Thus, the data suggests that poor nutrition increases the risk of postoperative PJI in patients undergoing TJA. It may be beneficial to comprehensively assess the nutritional status of suspected malnourished patients prior to elective TJA (22,25). Though the optimal method for addressing malnutrition has yet to be determined, treatment options include administration of high protein supplements, vitamin and mineral supplementation and increased caloric intake (26,31,32).

Hyperglycemia and uncontrolled diabetes mellitus

Diabetes mellitus is one of the most common disorders worldwide and the prevalence of diabetes has increased in the past few decades. Globally, 382 million people had diabetes in 2013 and that number is expected to rise to 592 million by 2035 (33). The number of diabetic patients undergoing TJA has also increased yearly, as diabetes significantly increases the risk of developing severe osteoarthritis (34,35). Yang *et al.* has reported that the

prevalence of diabetes among TKA patients was 12.2% (34).

Diabetes mellitus is a known, independent risk factor for developing PJI (8,9,34). Jämsen *et al.* reported that PJI occurred in 1.59% of THA and 2.19% of TKA patients with diabetes, compared to infection rates of 0.66% and 0.48%, respectively, in non-diabetic patients (17). The level of glycemic control has also been reported to influence the risk of PJI (22). Uncontrolled diabetes is defined as blood glucose levels greater than 200 mg/L or hemoglobin (Hgb) A1c levels greater than 7% (11). Marchant *et al.* compared uncontrolled diabetes, controlled diabetes, and non-diabetic patients and found that there was a significantly increased risk of developing a postoperative wound infection when diabetes was inadequately controlled [adjusted odds ratio (OR) =2.28; 95% confidence interval (CI), 1.36-3.81; P=0.002] (36).

Perioperative hyperglycemia is also a risk factor for PJI in arthroplasty patients, as blood glucose values greater than 200 mg/dL double the risk of PJI (37). Mraovic *et al.* reported that even patients without a diagnosis of diabetes were 3 times more likely to develop PJI if their postoperative day (POD) 1 blood glucose values were >140 mg/dL. PJI patients had significantly higher perioperative blood glucose values (PJI 112±36 mg/dL; non-PJI 105±31 mg/dL; P=0.043) and higher POD 1 blood glucose values (PJI 154±37 mg/dL; non-PJI 138±31 mg/dL; P<0.001). Additionally, there were significantly more diabetic patients in the infected group (22%) than the non-infected group (9%, P<0.001) (37). These results indicate that diabetes mellitus and perioperative blood glucose levels are predictors for PJI following TJA.

This increased risk of PJI in diabetics and hyperglycemic patients may be due to impaired defenses against bacteria, including reduced vascular permeability, oxygen delivery and redox reactions, neutrophil adherence, chemotaxis and phagocytosis of immune cells, functionality of antibody responses and complement proteins, and intracellular bactericidal activity (38). This can impair wound healing (39,40), as 1.2-12% of diabetic patients experience wound related complications following TJA (22). Likewise, elevated glucose levels may increase biofilm formation (41).

The role of HgbA1c in predicting the development of PJI has not yet been definitively confirmed and the literature for a HgbA1c cut off is controversial. Iorio *et al.* failed to report an association between HgbA1c values and susceptibility to infection, and concluded that HbA1c values may not be effective predictors for postoperative infection (42). Likewise, Kremers *et al.* reported that poor glycemic control, as assessed by HgbA1c levels, was not a good predictor of PJI risk (43). More recently, Chrastil *et al.* reported no increased risk of PJI associated with elevated HgbA1c (HR =0.86, P=0.23) (44).

However, several studies have indicated a specific cutoff value above which risk of postoperative infection increases significantly. The reported values vary between studies, but preoperative HgbA1c values of 7% (38), 7.5% (45), and 8% (46) have been suggested as cutoffs. Harris *et al.* also reported that preoperative HgbA1c ≥7% increased risk of postoperative complications. However, they suggest that this value of 7% should not be designated as a discrete threshold; optimizing a patient from 8.5% to 7.2% will reduce complication risk more than a reduction from 7.2% to 6.9% (47). Furthermore, enforcing a strict cutoff HgbA1c values above which elective surgery is delayed, especially if this value is too low, can postpone surgery for a number of patients who may not have otherwise experienced a postoperative complication (47). Giori *et al.* reported that 41% of diabetic patients whose surgery was delayed pending reduction of HgbA1c to ≤7% were unable to cross this threshold (48). A HgbA1c value of 8% may be a more realistic threshold value necessitating preoperative optimization for diabetic patients. While it is critical to optimize patients before elective TJA, increased risk of postoperative infection in patients with uncontrolled diabetes and perioperative hyperglycemia must be balanced against the fact that access to TJA could significantly improve their quality of life. Orthopaedic surgeons must work with their diabetic and hyperglycemic patients to decide how to balance these factors.

Rheumatoid arthritis (RA)

Nearly 5% of TJA patients have RA (24). Several studies have reported RA as an independent risk factor for PJI, with infection rates being higher in RA patients compared to patients without RA (HR =1.71 after THA and HR =1.18 after TKA) (7,8,17,49). The underlying mechanism causing this increased risk of infection has yet to be defined. However, reports suggest that the disease itself, associated comorbid conditions, and immunosuppressive therapies collectively contribute to increased PJI susceptibility (50).

Immunosuppressive therapies involving corticosteroids, such as prednisone, and disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, that inhibit tumor necrosis factor alpha (TNF-α) or interleukin 6 (IL-6) production place TJA patients with RA at greater risk

for postoperative infection (51-53). Decreased immunity with these medications increases the incidence of surgical wound complications like wound dehiscence, which may lead to PJI (54). Likewise, continued use of methotrexate therapy during the perioperative period has been shown to increase the rate of postoperative infection. Postoperative investigations by Carpenter *et al.* demonstrated that discontinuation of methotrexate one week before and after surgery significantly decreased the risk of PJI in RA patients undergoing elective TJA (55). However, there is some controversy surrounding this association, as some studies have reported no increase in the incidence of PJI, regardless of whether these treatments are discontinued perioperatively (56). Grennan *et al.* studied patients with RA undergoing elective orthopaedic surgery and reported that patients undergoing continued methotrexate treatment showed a significantly reduced infection rate compared to patients who discontinued methotrexate two weeks before and after surgery, suggesting that methotrexate treatment should not be stopped in RA patients before elective surgery (57).

Although there is a lack of consensus in the literature regarding the discontinuance of anti-rheumatic therapy before elective TJA, expert opinion seems to suggest the importance of cessation to reduce PJI risk. The American College of Rheumatology and the British Society for Rheumatology recommends withholding TNF-α inhibitors around the time of TJA (58-60). Likewise, the International Consensus Group (ICG) on Periprosthetic Joint Infection recommended stopping DMARDs prior to elective joint arthroplasty and developed a cessation schedule for different immunosuppressive agents (*Table 1*).

Table 1 Recommendation for cessation of anti-inflammatory agents prior to total joint arthroplasty

Recommendation	Half life	Medication
Continue therapy up to and including the surgery day	1-2 months	Hydroxychloroquine
Hold for at least 1.5 weeks prior to surgery	4.3 days	Etanercept
Hold for 3 weeks prior to surgery	8-10 days	Infliximab
Hold for 1 month prior to surgery	12-14 days	Abatacept; adalimumab; certolizumab; golimumab; tocilizumab
Hold for 6 weeks prior	~2 weeks	Leflunomide
Hold for 2 months prior	21 days	Rituximab
Discontinue 1 week prior to surgery	2-17 h	NSAIDs*
	1-2 h	Allopurinol
	26-32 h	Colchicine
	26-32 h	Probenecid
	5 h	Sulfasalazine
	7.6 h	Azathioprine
	0.7-5.8 h	Methotrexate[a]*

Adapted from Aggarwal *et al*. and Rezapoor *et al.* (26,58). [a], continue therapy 2 weeks after surgery, for patients with renal dysfunction, hold 2 weeks prior to surgery; *, controversial stop time.

Preoperative anemia

Preoperative anemia, defined as hemoglobin level less than 12 g/dL in women and less than 13 g/dL in men, frequently occurs in 15% to 33% of patients undergoing elective TJA (61). Patients with preoperative anemia are at greater risk for developing PJI (HR =1.36 after THA and HR =1.26 after TKA) (7,8). Out of 15,722 elective TJA patients, PJI occurred more frequently in anemic patients (4.3%) compared to non-anemic patients (2%, P<0.01). Multivariate analysis showed that the risk of PJI was higher in anemic patients than in non-anemic patients, identifying preoperative anemia as an independent risk factor for PJI (61).

The literature describing the pathophysiologic association between preoperative anemia and increased risk for PJI is limited. However, reports indicate that patients with preoperative anemia are more likely to receive perioperative allogeneic blood transfusions, which is associated with increased postoperative infection (62,63). Though it is costly, preoperatively prescribing recombinant human erythropoietin can decrease the perioperative need for transfusion, lowering the risk of subsequent joint infection (5,64). Conversely, orthopedists can preoperatively evaluate any other possible causes for anemia, such as iron deficiency, in order to minimize the risk of PJI (5,65,66).

Cardiovascular disorders

Several studies have indicated that cardiovascular disorders predispose arthroplasty patients to PJI (8,10,37). Bozic *et al.* reported that the following specific cardiovascular diseases can significantly predispose patients to PJI: congestive heart failure (HR =1.28), peripheral valvular disease (HR =1.13),

valvular disease (HR =1.15) and pulmonary circulation disorders (HR =1.42) (8). Pulido *et al.* reported that atrial fibrillation and myocardial infarction are independent comorbid factors associated with higher risks of infection, as well (10). These authors suggested that this increased risk of infection could be due to the fact that patients with cardiac disorders are more likely to receive aggressive anticoagulation (10).

For example, in patients with atrial fibrillation, the American College of Chest Physicians (ACCP) recommends high-dose aspirin or warfarin anticoagulation therapy. Warfarin therapy typically keeps the international normalized ratio (INR) in the range of 2.0-3.0, which significantly increases the risk of bleeding events after TJA. In a retrospective study examining atrial fibrillation and chronic anticoagulation therapy, Aggarwal *et al.* reported that patients with atrial fibrillation had a significantly higher prevalence of PJI (5.6% *vs.* 0.62%; P=0.02) (67).

To minimize the risk of PJI, patients with cardiovascular disorders should work with cardiologists to halt anticoagulation therapy and normalize INR levels (67). Patients with serious cardiovascular disorders tend to be older and may have increased problems with wound healing (10). These patients are at higher risk of infection and should be referred to a cardiologist for preoperative evaluation (8,10).

Chronic renal failure

Chronic renal failure is a growing problem worldwide. Patients suffering from chronic renal failure are initially treated with medications, though many ultimately require hemodialysis or renal transplantation (68). Long-term hemodialysis patients often develop β2-microglobulin amyloid deposition in and around joints, which invades the synovium, capsule, and cartilage and causes effusive arthropathy (68,69). Likewise, renal transplant patients receive life-long corticosteroid and immunosuppressive therapy, and are at greater risk of developing avascular necrosis of the femoral head (70-72). Thus, a significant number of patients with chronic renal failure develop degenerative joint disease and many eventually require TJA for erosive osteoarthritis, osteonecrosis, or following femoral neck fractures (69,73). In fact, these patients are 5 to 6 times more likely to require TJA than the general population (70,71).

Reports suggest that patients with chronic renal failure are also at a greater risk of developing PJI (HR =1.38 after TKA) (8,68,70,74). Interestingly, the risk of infection seems to be higher in hemodialysis patients than immunosuppressed transplant patients. Lieu *et al.* reported that hemodialysis patients had approximately twice the infection rate and higher rates of mortality than renal transplant patients (70). Likewise, Shrader *et al.* found that the PJI rate was 22% in hemodialysis patients and 8% in renal transplant patients (75). Notably, studies have shown that both groups showed increased rates of PJI compared to patients without chronic renal failure (70,75). Though several studies have reported that this increased infection rate is seen in both hemodialysis and renal transplant patients undergoing TJA, some studies suggest the opposite, reporting that there was no increased risk of infection in renal transplant patients following TJA (71,76-78). However, from the available data, it appears that chronic renal failure patients in both groups are at greater risk of developing PJI.

The exact cause of this increased risk of has yet to be determined, but it is likely multifactorial. Multiple combined comorbidities in these patients may collectively contribute to an increased infection rate (5,70). Additionally, the immunosuppressive nature of therapies associated with renal transplantation and hemodialysis could increase susceptibility to infection (70,74). Regardless of the pathophysiological association between chronic renal failure and PJI, it is imperative that in patients with renal failure, prophylaxis and treatment of infection is strictly monitored due to the potential nephrotoxicity from antibiotics (68).

Smoking

Smoking is known to be associated with increased postoperative morbidity and mortality (79). In arthroplasty patients, smoking reduces blood flow to the healing tissue and impairs delivery of humoral and cellular mechanisms of immunity to the surgical site (80,81). Nicotine in cigarettes releases catecholamines that lead to vasoconstriction and hypoperfusion and also increases local platelet aggregation and thrombi formation, which may further limit soft-tissue perfusion (82). Additionally, studies have demonstrated that nicotine in cigarettes has immunomodulatory effects, disrupting immune cell function and placing TJA patients at increased risk of developing a postoperative infection (83,84). Wound hypoxia associated with smoking also disturbs neutrophil defense mechanisms against pathogens and disrupts tissue repair (80,85). Tissue hypoxia can occur not only from vasoconstriction but also from inhaled carbon

monoxide in cigarette smoke (86). Carbon monoxide binds strongly to hemoglobin and forms carboxyhemoglobin, which has a high affinity for oxygen and significantly decreases oxygen delivery to healing tissues (87,88). As adequate oxygenation is essential for effective tissue repair, smoking significantly impairs soft tissue repair and wound healing, increasing susceptibility to infection (80).

Current smokers undergoing TJA showed significantly increased rates of surgical site infection (SSI) compared to nonsmokers (OR =1.41; 95% CI, 1.16-1.72) (89), and current smokers were more likely to experience wound complications than former smokers and nonsmokers (1.8% compared to 1.3% and 1.1%, respectively; P<0.001) (90). Current smoker status was also identified as a significant risk factor for wound infection, as current smokers had approximately twice the rate of deep wound infection compared with former smokers or nonsmokers (91). These findings support reports that current smoking at the time of elective TJA is associated with increased rates of postoperative wound infection (79,92-94).

While smoking increases the risk of infection, discontinuing smoking prior to surgery has been shown to reduce the risk of postoperative complications [relative risk (RR) =0.76; 95% CI, 0.69-0.84], especially complications related to poor wound healing (95). Although an optimal period of preoperative smoking cessation has yet to be established, most reports suggest a period of 4 to 8 weeks is effective (93,94,96-98). Tønnesen *et al.* reported that, in smokers, immune function is restored after 4-6 weeks of abstinence and wound healing capability is restored after 3-4 weeks (99). Longer periods of preoperative smoking cessation, however, have also been associated with lower rates of postoperative infection and preoperative cessation periods of up to 6 months have also been suggested (83,100). Abrupt reduction in cigarette consumption is rarely permanently successful in terms of smoking cessation. However, individual counseling, self-help groups, nicotine-replacement therapy and physician advising are proven techniques that promote prolonged cessation (97,100). Tobacco use and history of smoking should be preoperatively evaluated and smoking cessation should be highly encouraged in order to optimize the patient prior to TJA and lower the risk of SSI and PJI.

Alcohol abuse

Excessive alcohol consumption (greater than 40 units per week) increases the risk of postoperative complications, including episodes of excessive bleeding and infection (99,101). Bradley *et al.* evaluated 9,176 male United States veterans who underwent major, non-cardiac surgery and reported that excessive alcohol consumption significantly increased the risk of developing infection (102). Postoperative complications associated with alcohol abuse are the result of alcohol-induced disruptions of the immune response and the metabolic stress response that augment the physiological stress from the surgical procedure (99). Consuming 2-3 drinks daily disrupts the function of the immune response, manifested as significantly suppressed delayed type hypersensitivity (DTH) (103,104).

Although alcohol cessation has not been demonstrated to reduce the risk of PJI prior to elective TJA, several studies have reported reduced morbidity after a period of abstinence (103,105). DTH is significantly improved after a 2-week period of abstinence and restored to normal after 8 weeks. In alcoholics, immune competence is recovered after 2-6 weeks of alcohol cessation (106) and wound-healing capability is restored after 3-4 weeks of cessation (107). Furthermore, Tønnesen *et al.* reported that alcohol cessation 4 weeks prior to surgery significantly reduced postoperative morbidity in alcohol abusers (99).

A history of alcohol consumption should be preoperatively evaluated and a cessation period of at least 4 weeks prior to surgery should be recommended for alcoholic arthroplasty patients in order to reverse physiological abnormalities associated with excessive alcohol consumption that increase the risk of PJI (58,105).

Depression

Bozic *et al.* identified depression as an independent risk factor for PJI (HR =1.28) (8). Though the pathophysiology of this association is unknown, physiologic depression and psychosis may be associated with malnutrition and subsequent need for allogeneic blood transfusion, which are separate risk factors for PJI (8,108). Furthermore, depression has a direct effect on the immune system, leaving patients more susceptible to infection (58). Because depression places patients at a greater risk for developing PJI, it may be beneficial to integrate evaluation of depression into the initial medical screening before elective TJA and to delay the elective procedure until depression is well managed (58,109).

Conclusions

There are many medical risk factors associated with the

Table 2 Patient-related medical risk factors for periprosthetic joint infection

Risk factor	Link to PJI	Intervention	Goal
Morbid obesity	Prolonged operative time, increased risk of poor wound healing, paradoxical malnutrition, presence of other medical comorbidities	Diet and exercise, bariatric surgery	BMI ≤40 kg/m^2
Malnutrition	Poor wound healing and persistent wound drainage	Administration of protein, vitamin and mineral supplementation; increased caloric intake	Serum albumin levels ≥3.5 g/dL; Serum transferrin levels ≥200 mg/dL; Serum prealbumin levels ≥15 mg/dL; TLC ≥1,500 cells/mm^3
Hyperglycemia and uncontrolled diabetes mellitus	Advanced glycation end products, decreased bacterial defenses	Diet and exercise, insulin	HgbA1c ≤8%, blood glucose ≤200 mg/dL
Rheumatoid arthritis	Immunosuppressive therapies (corticosteroids and DMARDs), increased rate of surgical wound complications, presence of other medical comorbidities	Perioperative cessation of immunosuppressive therapies	
Preoperative anemia	Increased need for allogeneic blood transfusions	Preoperatively screen for other possible causes of anemia (i.e. iron deficiency), preoperative administration of recombinant human erythropoietin	Hgb ≥12 g/dL in women and 13 g/dL in men
Cardiovascular disorder	Chronic anticoagulation therapy and increased INR; increased risk of would related complications and poor wound healing	Perioperative cessation of anticoagulation therapy, preoperative evaluation by cardiologist	INR level ≤2
Chronic renal failure	Presence of other medical comorbidities, immunosuppressive nature of therapy (hemodialysis and renal transplantation)	Preoperative evaluation of patient by nephrologist, postoperative management of renal function	
Smoking	Hypoperfusion, platelet aggregation and formation of thrombi, wound hypoxia, poor wound healing, decreased immune defenses	Preoperative evaluation of smoking history, perioperative smoking cessation, individual counseling, physician advising, NTR	
Alcohol abuse	Protein deficiency and malnutrition, diminished host immunity, impaired wound healing	Preoperative evaluation of alcohol history, perioperative alcohol cessation	
Depression	Presence of other medical comorbidities (i.e., malnutrition and need for allogeneic blood transfusion); immunomodulatory effects	Evaluation of depression during preoperative medical screening, treatment of depression prior to surgery	

PJI, periprosthetic joint infection; BMI, body mass index; DMARD, disease-modifying anti-rheumatic drugs; Hgb, hemoglobin; INR, international normalized ratio; TLC, total lymphocyte count; NTR, nicotine replacement therapy.

development of PJI following TJA. Since TJA is an elective surgery, this allows orthopaedic surgeons to medically optimize patients prior to surgery to minimize their risk of developing a postoperative infection (*Table 2*). Although a number of risk factors for PJI have been identified in the literature, the evidence is too limited for many of these risk factors to be able to determine their full association with PJI after TJA. There is a need for further, high-quality research studies to strengthen this limited evidence so that high-risk patients can be more effectively counseled and optimized preoperatively. It is important to remember that no TJA patient is free of risk, and there are certain risk factors for PJI that have yet to be identified; however, knowledge and understanding of these known risk factors can help orthopaedic surgeons to minimize such risks in order to reduce the incidence of infection.

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Footnote

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References

1. Bozic KJ, Ward DT, Lau EC, et al. Risk factors for periprosthetic joint infection following primary total hip arthroplasty: a case control study. J Arthroplasty 2014;29:154-6.
2. Kurtz S, Ong K, Lau E, et al. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780-5.
3. Havelin LI, Fenstad AM, Salomonsson R, et al. The Nordic Arthroplasty Register Association: a unique collaboration between 3 national hip arthroplasty registries with 280,201 THRs. Acta Orthop 2009;80:393-401.
4. Maier GS, Horas K, Seeger JB, et al. Is there an association between periprosthetic joint infection and low vitamin D levels? Int Orthop 2014;38:1499-504.
5. Baek SH. Identification and preoperative optimization of risk factors to prevent periprosthetic joint infection. World J Orthop 2014;5:362-7.
6. Phillips JE, Crane TP, Noy M, et al. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey. J Bone Joint Surg Br 2006;88:943-8.
7. Bozic KJ, Lau E, Kurtz S, et al. Patient-related risk factors for periprosthetic joint infection and postoperative mortality following total hip arthroplasty in Medicare patients. J Bone Joint Surg Am 2012;94:794-800.
8. Bozic KJ, Lau E, Kurtz S, et al. Patient-related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. Clin Orthop Relat Res 2012;470:130-7.
9. Lai K, Bohm ER, Burnell C, et al. Presence of medical comorbidities in patients with infected primary hip or knee arthroplasties. J Arthroplasty 2007;22:651-6.
10. Pulido L, Ghanem E, Joshi A, et al. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res 2008;466:1710-5.
11. Daines BK, Dennis DA, Amann S. Infection prevention in total knee arthroplasty. J Am Acad Orthop Surg 2015;23:356-64.
12. Arsoy D, Woodcock JA, Lewallen DG, et al. Outcomes and complications following total hip arthroplasty in the super-obese patient, BMI > 50. J Arthroplasty 2014;29:1899-905.
13. Dowsey MM, Choong PF. Obesity is a major risk factor for prosthetic infection after primary hip arthroplasty. Clin Orthop Relat Res 2008;466:153-8.
14. Dowsey MM, Choong PF. Obese diabetic patients are at substantial risk for deep infection after primary TKA. Clin Orthop Relat Res 2009;467:1577-81.
15. Malinzak RA, Ritter MA, Berend ME, et al. Morbidly obese, diabetic, younger, and unilateral joint arthroplasty patients have elevated total joint arthroplasty infection rates. J Arthroplasty 2009;24:84-8.
16. Chen J, Cui Y, Li X, et al. Risk factors for deep infection after total knee arthroplasty: a meta-analysis. Arch Orthop Trauma Surg 2013;133:675-87.
17. Jämsen E, Nevalainen P, Eskelinen A, et al. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single-center analysis of 7181 primary hip and knee replacements for osteoarthritis. J Bone Joint Surg Am 2012;94:e101.
18. Liabaud B, Patrick DA Jr, Geller JA. Higher body mass index leads to longer operative time in total knee arthroplasty. J Arthroplasty 2013;28:563-5.
19. Jibodh SR, Gurkan I, Wenz JF. In-hospital outcome and resource use in hip arthroplasty: influence of body mass. Orthopedics 2004;27:594-601.
20. Namba RS, Paxton L, Fithian DC, et al. Obesity and perioperative morbidity in total hip and total knee arthroplasty patients. J Arthroplasty 2005;20:46-50.
21. Patel VP, Walsh M, Sehgal B, et al. Factors associated with prolonged wound drainage after primary total hip and knee arthroplasty. J Bone Joint Surg Am 2007;89:33-8.
22. Zmistowski B, Tetreault MW, Alijanipour P, et al. Recurrent periprosthetic joint infection: persistent or new infection? J Arthroplasty 2013;28:1486-9.
23. McElroy MJ, Pivec R, Issa K, et al. The effects of obesity and morbid obesity on outcomes in TKA. J Knee Surg 2013;26:83-8.
24. Berbari EF, Hanssen AD, Duffy MC, et al. Risk factors for prosthetic joint infection: case-control study. Clin Infect Dis 1998;27:1247-54.
25. Greene KA, Wilde AH, Stulberg BN. Preoperative nutritional status of total joint patients. Relationship to postoperative wound complications. J Arthroplasty 1991;6:321-5.
26. Aggarwal VK, Tischler EH, Lautenbach C, et al.

Mitigation and education. J Arthroplasty 2014;29:19-25.
27. Yi PH, Frank RM, Vann E, et al. Is potential malnutrition associated with septic failure and acute infection after revision total joint arthroplasty? Clin Orthop Relat Res 2015;473:175-82.
28. Jaberi FM, Parvizi J, Haytmanek CT, et al. Procrastination of wound drainage and malnutrition affect the outcome of joint arthroplasty. Clin Orthop Relat Res 2008;466:1368-71.
29. Cross MB, Yi PH, Thomas CF, et al. Evaluation of malnutrition in orthopaedic surgery. J Am Acad Orthop Surg 2014;22:193-9.
30. Nawabi DH, Chin KF, Keen RW, et al. Vitamin D deficiency in patients with osteoarthritis undergoing total hip replacement: a cause for concern? J Bone Joint Surg Br 2010;92:496-9.
31. Nicholson JA, Dowrick AS, Liew SM. Nutritional status and short-term outcome of hip arthroplasty. J Orthop Surg (Hong Kong) 2012;20:331-5.
32. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. JAMA. 2002;287:3127-9.
33. Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014;103:137-49.
34. Yang Z, Liu H, Xie X, et al. The influence of diabetes mellitus on the post-operative outcome of elective primary total knee replacement: a systematic review and meta-analysis. Bone Joint J 2014;96-B:1637-43.
35. Schett G, Kleyer A, Perricone C, et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study. Diabetes Care 2013;36:403-9.
36. Marchant MH Jr, Viens NA, Cook C, et al. The impact of glycemic control and diabetes mellitus on perioperative outcomes after total joint arthroplasty. J Bone Joint Surg Am 2009;91:1621-9.
37. Mraovic B, Suh D, Jacovides C, et al. Perioperative hyperglycemia and postoperative infection after lower limb arthroplasty. J Diabetes Sci Technol 2011;5:412-8.
38. Dronge AS, Perkal MF, Kancir S, et al. Long-term glycemic control and postoperative infectious complications. Arch Surg 2006;141:375-80; discussion 380.
39. McMurry JF Jr. Wound healing with diabetes mellitus. Better glucose control for better wound healing in diabetes. Surg Clin North Am 1984;64:769-78.
40. Goodson WH 3rd, Hung TK. Studies of wound healing in experimental diabetes mellitus. J Surg Res 1977;22:221-7.
41. Seneviratne CJ, Yip JW, Chang JW, et al. Effect of culture media and nutrients on biofilm growth kinetics of laboratory and clinical strains of Enterococcus faecalis. Arch Oral Biol 2013;58:1327-34.
42. Iorio R, Williams KM, Marcantonio AJ, et al. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. J Arthroplasty 2012;27:726-9.e1.
43. Maradit Kremers H, Lewallen LW, Mabry TM, et al. Diabetes mellitus, hyperglycemia, hemoglobin A1C and the risk of prosthetic joint infections in total hip and knee arthroplasty. J Arthroplasty 2015;30:439-43.
44. Chrastil J, Anderson MB, Stevens V, et al. Is Hemoglobin A1c or Perioperative Hyperglycemia Predictive of Periprosthetic Joint Infection or Death Following Primary Total Joint Arthroplasty? J Arthroplasty 2015;30:1197-202.
45. Goldstein DT, Durinka JB, Martino N, et al. Effect of preoperative hemoglobin A(1c) level on acute postoperative complications of total joint arthroplasty. Am J Orthop (Belle Mead NJ) 2013;42:E88-90.
46. Hwang JS, Kim SJ, Bamne AB, et al. Do glycemic markers predict occurrence of complications after total knee arthroplasty in patients with diabetes? Clin Orthop Relat Res 2015;473:1726-31.
47. Harris AH, Bowe TR, Gupta S, et al. Hemoglobin A1C as a marker for surgical risk in diabetic patients undergoing total joint arthroplasty. J Arthroplasty 2013;28:25-9.
48. Giori NJ, Ellerbe LS, Bowe T, et al. Many diabetic total joint arthroplasty candidates are unable to achieve a preoperative hemoglobin A1c goal of 7% or less. J Bone Joint Surg Am 2014;96:500-4.
49. Schrama JC, Espehaug B, Hallan G, et al. Risk of revision for infection in primary total hip and knee arthroplasty in patients with rheumatoid arthritis compared with osteoarthritis: a prospective, population-based study on 108,786 hip and knee joint arthroplasties from the Norwegian Arthroplasty Register. Arthritis Care Res (Hoboken) 2010;62:473-9.
50. Tande AJ, Patel R. Prosthetic joint infection. Clin Microbiol Rev 2014;27:302-45.
51. Giles JT, Bartlett SJ, Gelber AC, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Rheum 2006;55:333-7.
52. Momohara S, Kawakami K, Iwamoto T, et al. Prosthetic joint infection after total hip or knee arthroplasty in rheumatoid arthritis patients treated with nonbiologic and biologic disease-modifying antirheumatic drugs. Mod Rheumatol 2011;21:469-75.

53. Kawakami K, Ikari K, Kawamura K, et al. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-alpha blockers: perioperative interruption of tumour necrosis factor-alpha blockers decreases complications? Rheumatology (Oxford) 2010;49:341-7.
54. White RH, McCurdy SA, Marder RA. Early morbidity after total hip replacement: rheumatoid arthritis versus osteoarthritis. J Gen Intern Med 1990;5:304-9.
55. Carpenter MT, West SG, Vogelgesang SA, et al. Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. Orthopedics 1996;19:207-10.
56. Perhala RS, Wilke WS, Clough JD, et al. Local infectious complications following large joint replacement in rheumatoid arthritis patients treated with methotrexate versus those not treated with methotrexate. Arthritis Rheum 1991;34:146-52.
57. Grennan DM, Gray J, Loudon J, et al. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Ann Rheum Dis 2001;60:214-7.
58. Rezapoor M, Parvizi J. Prevention of Periprosthetic Joint Infection. J Arthroplasty 2015;30:902-7.
59. Ding T, Ledingham J, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology (Oxford) 2010;49:2217-9.
60. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762-84.
61. Greenky M, Gandhi K, Pulido L, et al. Preoperative anemia in total joint arthroplasty: is it associated with periprosthetic joint infection? Clin Orthop Relat Res 2012;470:2695-701.
62. Marik PE. The hazards of blood transfusion. Br J Hosp Med (Lond) 2009;70:12-5.
63. Borghi B, Casati A. Incidence and risk factors for allogenic blood transfusion during major joint replacement using an integrated autotransfusion regimen. The Rizzoli Study Group on Orthopaedic Anaesthesia. Eur J Anaesthesiol 2000;17:411-7.
64. Moonen AF, Thomassen BJ, Knoors NT, et al. Pre-operative injections of epoetin-alpha versus post-operative retransfusion of autologous shed blood in total hip and knee replacement: a prospective randomised clinical trial. J Bone Joint Surg Br 2008;90:1079-83.
65. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology 2010;113:482-95.
66. Myers E, O'Grady P, Dolan AM. The influence of preclinical anaemia on outcome following total hip replacement. Arch Orthop Trauma Surg 2004;124:699-701.
67. Aggarwal VK, Tischler EH, Post ZD, et al. Patients with atrial fibrillation undergoing total joint arthroplasty increase hospital burden. J Bone Joint Surg Am 2013;95:1606-11.
68. Tornero E, Riba J, Garcia-Ramiro S. Special issues involving periprosthetic infection in immunodeficiency patients. Open Orthop J 2013;7:211-8.
69. Ford PM. Arthropathies associated with renal disease including dialysis-related amyloid. Curr Opin Rheumatol 1992;4:63-7.
70. Lieu D, Harris IA, Naylor JM, et al. Review article: Total hip replacement in haemodialysis or renal transplant patients. J Orthop Surg (Hong Kong) 2014;22:393-8.
71. Nowicki P, Chaudhary H. Total hip replacement in renal transplant patients. J Bone Joint Surg Br 2007;89:1561-6.
72. Marston SB, Gillingham K, Bailey RF, et al. Osteonecrosis of the femoral head after solid organ transplantation: a prospective study. J Bone Joint Surg Am 2002;84-A:2145-51.
73. Goldstein S, Winston E, Chung TJ, et al. Chronic arthropathy in long-term hemodialysis. Am J Med 1985;78:82-6.
74. McCleery MA, Leach WJ, Norwood T. Rates of infection and revision in patients with renal disease undergoing total knee replacement in Scotland. J Bone Joint Surg Br 2010;92:1535-9.
75. Shrader MW, Schall D, Parvizi J, et al. Total hip arthroplasty in patients with renal failure: a comparison between transplant and dialysis patients. J Arthroplasty 2006;21:324-9.
76. Chmell SJ, Schwartz CM, Giacchino JL, et al. Total hip replacement in patients with renal transplants. Arch Surg 1983;118:489-95.
77. Deo S, Gibbons CL, Emerton M, et al. Total hip replacement in renal transplant patients. J Bone Joint Surg Br 1995;77:299-302.
78. Radford PJ, Doran A, Greatorex RA, et al. Total hip replacement in the renal transplant recipient. J Bone Joint Surg Br 1989;71:456-9.

79. Sadr Azodi O, Bellocco R, Eriksson K, et al. The impact of tobacco use and body mass index on the length of stay in hospital and the risk of post-operative complications among patients undergoing total hip replacement. J Bone Joint Surg Br 2006;88:1316-20.
80. Sørensen LT, Jørgensen S, Petersen LJ, et al. Acute effects of nicotine and smoking on blood flow, tissue oxygen, and aerobe metabolism of the skin and subcutis. J Surg Res 2009;152:224-30.
81. Padmavathi P, Reddy VD, Maturu P, et al. Smoking-induced alterations in platelet membrane fluidity and Na(+)/K(+)-ATPase activity in chronic cigarette smokers. J Atheroscler Thromb 2010;17:619-27.
82. Zevin S, Gourlay SG, Benowitz NL. Clinical pharmacology of nicotine. Clin Dermatol 1998;16:557-64.
83. Argintar E, Triantafillou K, Delahay J, et al. The musculoskeletal effects of perioperative smoking. J Am Acad Orthop Surg 2012;20:359-63.
84. Mehta H, Nazzal K, Sadikot RT. Cigarette smoking and innate immunity. Inflamm Res 2008;57:497-503.
85. Hopf HW, Hunt TK, West JM, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg 1997;132:997-1004; discussion 1005.
86. Kapadia BH, Johnson AJ, Naziri Q, et al. Increased revision rates after total knee arthroplasty in patients who smoke. J Arthroplasty 2012;27:1690-5.e1.
87. Heliövaara M, Karvonen MJ, Vilhunen R, et al. Smoking, carbon monoxide, and atherosclerotic diseases. Br Med J 1978;1:268-70.
88. Moucha CS, Clyburn T, Evans RP, et al. Modifiable risk factors for surgical site infection. J Bone Joint Surg Am 2011;93:398-404.
89. Singh JA, Houston TK, Ponce BA, et al. Smoking as a risk factor for short-term outcomes following primary total hip and total knee replacement in veterans. Arthritis Care Res (Hoboken) 2011;63:1365-74.
90. Duchman KR, Gao Y, Miller BJ. Prognostic factors for survival in patients with Ewing's sarcoma using the surveillance, epidemiology, and end results (SEER) program database. Cancer Epidemiol 2015;39:189-95.
91. Duchman KR, Gao Y, Pugely AJ, et al. The Effect of Smoking on Short-Term Complications Following Total Hip and Knee Arthroplasty. J Bone Joint Surg Am 2015;97:1049-58.
92. Myers K, Hajek P, Hinds C, et al. Stopping smoking shortly before surgery and postoperative complications: a systematic review and meta-analysis. Arch Intern Med 2011;171:983-9.
93. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Ann Surg 2003;238:1-5.
94. Lindström D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: a randomized trial. Ann Surg 2008;248:739-45.
95. Mills E, Eyawo O, Lockhart I, et al. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. Am J Med 2011;124:144-54.e8.
96. Møller AM, Villebro N, Pedersen T, et al. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. Lancet 2002;359:114-7.
97. Bushnell BD, Horton JK, McDonald MF, et al. Perioperative medical comorbidities in the orthopaedic patient. J Am Acad Orthop Surg 2008;16:216-27.
98. Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation. Cochrane Database Syst Rev 2014;3:CD002294.
99. Tønnesen H, Nielsen PR, Lauritzen JB, et al. Smoking and alcohol intervention before surgery: evidence for best practice. Br J Anaesth 2009;102:297-306.
100. Potter GD, Rao N, Mabry TM. Prevention of periprosthetic joint infection. In: Springer BD, Parvizi J, editors. Periprosthetic Joint Infection of the Hip and Knee. New York: Springer-Verlag; 2013:41-51.
101. Harris AH, Reeder R, Ellerbe L, et al. Preoperative alcohol screening scores: association with complications in men undergoing total joint arthroplasty. J Bone Joint Surg Am 2011;93:321-7.
102. Bradley KA, Rubinsky AD, Sun H, et al. Alcohol screening and risk of postoperative complications in male VA patients undergoing major non-cardiac surgery. J Gen Intern Med 2011;26:162-9.
103. Tønnesen H. Alcohol abuse and postoperative morbidity. Dan Med Bull 2003;50:139-60.
104. Pietsch JB, Meakins JL. Predicting infection in surgical patients. Surg Clin North Am 1979;59:185-97.
105. Tonnesen H, Rosenberg J, Nielsen HJ, et al. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial. BMJ 1999;318:1311-6.
106. Zeidel A, Beilin B, Yardeni I, et al. Immune response in asymptomatic smokers. Acta Anaesthesiol Scand

2002;46:959-64.
107. Whiteford L. Nicotine, CO and HCN: the detrimental effects of smoking on wound healing. Br J Community Nurs 2003;8:S22-6.
108. Leonard BE. The immune system, depression and the action of antidepressants. Prog Neuropsychopharmacol Biol Psychiatry 2001;25:767-80.
109. Kim KW, Han JW, Cho HJ, et al. Association between comorbid depression and osteoarthritis symptom severity in patients with knee osteoarthritis. J Bone Joint Surg Am 2011;93:556-63.

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