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Periprosthetic Joint Infection in Patients with Inflammatory Joint Disease: Prevention and Diagnosis

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Abstract

Purpose of Review—Periprosthetic joint infection (PJI) is a devastating complication that can occur following total joint arthroplasty (TJA), causing significant morbidity and often requiring revision surgery. This goal of this manuscript is to review the current evidence for the prevention and diagnosis of PJI in patients with inflammatory arthritis.

Recent Findings—Patients with inflammatory arthritis have a higher risk of PJI after TJA; however, there are several preventive, diagnostic, and therapeutic measures that can be optimized to lower the burden of PJI in this population. This manuscript will review the current evidence and clinical practice recommendations that support specific features of preoperative evaluation, perioperative medication management, and surgical planning in inflammatory arthritis patients undergoing TJA. Evidence and recommendations for the diagnosis of PJI in this patient population will also be reviewed.

Summary—Despite increased research efforts directed towards PJI, specific approaches directed at the inflammatory arthritis patient population remain surprisingly limited. Optimization strategies such as adequately managing disease-modifying medications, treating preoperative anemia, encouraging smoking cessation, and improving weight management are strongly encouraged before entering the perioperative period. If PJI does occur in the inflammatory arthritis patient, establishing the diagnosis is challenging, since guidelines were created from investigations of PJI in primarily patients without inflammatory arthritis. Future prospective research is required to better guide clinicians in preventing and diagnosing PJI in inflammatory arthritis patients undergoing TJA.

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Conflict of Interest Ajay Premkumar, Kyle Morse, Ashley E. Levack, and Alberto V. Carli declare that they have no conflict of interest.

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Keywords

Prosthetic joint infection; Rheumatoid; Inflammatory arthritis; Peri-operative management; Total knee arthroplasty; Total hip arthroplasty

Introduction

Total joint arthroplasty (TJA) is widely considered to be one of the great medical advancements of the past half-century, consistently relieving patients of pain, restoring mobility, and improving their quality of life [1-3]. Unfortunately, approximately 1% of all TJA patients develop a periprosthetic joint infection (PJI) following surgery, a devastating complication that has severe health and socioeconomic implications. The development of PJI following TJA of the hip or knee is associated with a 5-year mortality rate which is higher than that of breast cancer, melanoma, Hodgkin's lymphoma, and several other common malignancies [4]. In addition to increased morbidity and mortality, the cost of treating PJI is substantial, with treatment in the USA alone projected to cost over $1.6 billion per year by 2020 [5]. Given that the estimated prevalence of hip and knee TJA surgeries is estimated to increase by 145% by 2030, the societal cost of PJI can no longer be ignored [6].

Patients with inflammatory joint diseases such as rheumatoid arthritis (RA), juvenile inflammatory arthritis, ankylosing spondylitis, and psoriatic arthritis are known to be at higher risk for developing PJI following TJA [7]. This increased risk of infection is concerning given that significant advances in the medical management of patients with inflammatory joint disease have consequently led to increased activity levels, life expectancy, and ultimately a higher need for TJA [8]. Prior studies have demonstrated a 1.6–8 times higher risk of PJI in patients with inflammatory arthritis compared to patients with osteoarthritis, with one large review demonstrating an absolute risk increase of PJI from 0.84% in patients with osteoarthritis to 1.26% in patients with RA [9-11].

In addition to inflammatory joint disease, there are several other known independent risk factors for PJI, including increasing age, obesity, alcohol abuse, diabetes, smoking, malnutrition, American Society of Anesthesiologists (ASA) scale > 2, systemic and local corticosteroid therapy, blood transfusion, and immunosuppression, among others [12-14]. As many patients with inflammatory joint disease are treated with immunosuppressive therapies including corticosteroids and disease-modifying antirheumatic drugs (DMARDs), they are at higher risk of PJI [15]. The goal of this review is to delineate modifiable risk factors for PJI in patients with inflammatory arthritis. We also present and discuss the current evidence and guidelines regarding risk reduction strategies for PJI and diagnosis of PJI in this high-risk population.

Pre-Surgical Assessment and Optimization

Perioperative Management of Common Medications in the Rheumatologic Patient

Most therapeutic medications for inflammatory arthritis are immunosuppressive, delaying wound healing and increasing the perioperative risk of infection. However, halting these medications for a prolonged period of time could lead to an inflammatory "flare-up" of

arthritic symptoms, which impair postoperative rehabilitation and recovery. Therefore, a good understanding of how to manage these medications during the perioperative period is essential for the treating physician. The most common medications that require careful management include biological and non-biological DMARDs, corticosteroids, and other immunomodulators.

There is a paucity of level I data regarding the perioperative management of these medications. A 2017 practice guideline on the perioperative management of antirheumatic drugs was published through collaboration between the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons (AAHKS). These guidelines were developed through expert opinions and consensus from panels that included orthopedic surgeons, rheumatologists, infectious disease specialists, and patients [16••]. The major conclusions from these guidelines are (Table 1):

1. Non-biologic DMARDs do not need to be stopped perioperatively
2. Biologic DMARDs should be withheld as close to 1 dosing cycle as scheduling permits prior to surgery, and restarted after evidence of wound healing postoperatively (typically 14 days postoperatively) [16••, 17]

The dosing cycle, directly related to a medication's pharmacokinetic half-life, of each medication is listed in Table 1. For example, as secukinumab is dosed every 4 weeks, surgery should be scheduled 4 weeks after the last dose.

Skin Assessment

The two primary sources of bacteria that cause PJI are contiguous spread of skin flora into the surgical wound and, less commonly, hematogenous seeding from gastrointestinal, respiratory, urological, oral, or cutaneous sites. *Staphylococcus epidermis* is the most common pathogen across all cases of PJI and *Staphylococcus aureus* is the most common pathogen in patients with RA [17]. Due to the common involvement of skin flora in PJI, the Centers for Disease Control (CDC) recommend patients take a bath in a skin de-colonizing agent, such as chlorhexidine gluconate or antiseptic soap, at least once on the night prior to surgery to reduce the bacterial load at the surgical site [18].

For patients with psoriatic arthritis, a thorough skin assessment is necessary to characterize the location and extent of psoriatic plaques and surgeons should make every attempt to avoid making surgical incisions in proximity or through an active psoriatic plaque [19]. Despite differing opinions between dermatologists and orthopedic surgeons regarding the danger of incising active psoriatic plaques, high levels of bacteria have been consistently demonstrated to reside in these plaques, including *streptococcal* and *staphylococcal* species. This factor may be responsible for the relatively high deep surgical site infection rates (5–17%) noted in early studies in this patient population [20-22]. Preoperatively, skin lesions may be managed with topical betamethasone propionate plus vitamin D ointment such as calcipotriene, and while complete clearing of plaques may not occur, skin optimization is recommended prior to elective TJA [23].

Anemia

Anemia is the most common comorbidity in patients with rheumatoid arthritis with an estimated prevalence of 33.3 to 59.1% [24-27]. Preoperative anemia may increase the likelihood of allogenic transfusion following total joint arthroplasty, which in turn carries an increased risk of PJI [24-26, 28]. The most common causes of anemia in this population are anemia secondary to iron deficiency or chronic disease due to decreased erythropoiesis [25, 26].

Ogbemudia et al. [24] conducted a retrospective review of RA patients undergoing lower extremity TJA to assess the risk factors for postoperative transfusion and identify high-risk patients. In their cohort, all patients with a preoperative hemoglobin less than 9 g/dL received a transfusion postoperatively, and for every 0.1 g/dL increase in hemoglobin, there was an 8.3% decrease in the probability of requiring a transfusion postoperatively [24]. This study also identified three risk groups for postoperative transfusion: high risk (hemoglobin less than 9.0 g/dL), moderate risk (hemoglobin between 9.0 to 11.9 g/dL), and low risk (hemoglobin greater than 12.0 g/dL) [24]. Furthermore, patients with a history of myocardial infarction and those who have received a blood transfusion in the past were independently more likely to require postoperative transfusions [24]. Similarly, Aderinto and Brenkel [29] found a 70% chance of postoperative transfusion with a hemoglobin less than 12.0 g/dL in their general cohort of patients undergoing total hip arthroplasty.

No universal transfusion protocol exists for patients with inflammatory arthritis undergoing total joint arthroplasty. Nevertheless, iron and vitamin deficiencies should be corrected through supplementation strategies prior to surgery [26]. Although there is no published guideline specifically for preoperative transfusion in patients with inflammatory arthritis, administration of recombinant erythropoietin can increase preoperative hemoglobin levels and perioperative use of tranexamic acid has been associated with less blood loss during surgery [26, 30-32]. Postoperatively, little consensus exists regarding an ideal transfusion threshold for patients who have undergone TJA. A recent meta-analysis identified lower cardiovascular postoperative complications with a more liberal hemoglobin transfusion threshold of 10 g/dL compared with a more restrictive threshold of 8 g/dL [33•].

BMI and Diabetes

Body mass index (BMI) is a well-recognized risk factor for postoperative complications following TJA. Gandhi et al. [34] identified obesity (BMI >30) as a risk factor for decreased functional improvement following TJA of the hip or knee at 1 year in non-rheumatologic patients. With regard to infection, several well-powered studies have identified elevated BMI as a significant risk factor for surgical site infection, with one series identifying an eightfold increase in serious complications including PJI in patients whose BMI exceeded 50 [35•, 36-38]. Furthermore, Somayaji et al. [39] reported that patients with a BMI less than 18.5 kg/m^2 had an odds ratio of 6.0 (95% CI1.2– 30.9) for risk of surgical site infection compared to normal BMI controls. Although variability exists in BMI thresholds used between providers, patients with a BMI below 18.5 or over 40 kg/m^2 should be referred for nutritional counseling and medical weight management prior to undergoing TJA [35•]. Although the universal denial of TJA based on BMI is unwarranted, a reasonable goal of

achieving a BMI of less than 40 kg/m^2 should be attempted prior undergoing surgery [35•, 40].

Diabetes mellitus has been shown to be an independent predictor for generalized infection in the rheumatoid patient, with a reported hazard ratio of 1.6 (95% CI 1.12–2.30) [41]. Hemoglobin A1c has been identified as a key predictor for infection risk prior to TJA. Tarabichi et al. [42•] identified significant associations between preoperative hemoglobin A1c (HbA1c) levels and PJI risk, reporting that a HbA1c exceeding 7.7% carried an odds ratio of 1.6 (95% CI 1.26–2.11) for developing PJI compared to non-infection controls [42•]. This recent report as well as several other large cohort studies have led the American Diabetes Association to strongly recommend lowering preoperative HbA1c to less than 7% prior to elective surgery [43]. These guidelines do not make provisions with patients with inflammatory arthritis and, to date, few studies have precisely examined the association between preoperative HbA1C levels and PJI risk in this population.

Periodontitis

Periodontitis is common in rheumatoid arthritis patients with an estimated prevalence between 63.6–70.0%, and *S. aureus* is found in the flora of 56% of patients with RA [26, 44-49]. Additionally, Fuggle et al. [50] found an odds ratio of 1.13 (95% CI 1.04–1.23) for an increased risk of periodontitis in patients with RA compared to healthy controls. Proper dental care is warranted for all patients prior to undergoing TJA to minimize the risk for PJI. Historically, antibiotic prophylaxis before dental procedures was recommended to reduce hematogenous bacterial load in patients with a TJA. Specifically, some authors recommended that patients should take 2 g of either amoxicillin, cephalexin, or cephradine 1 h prior to the dental procedure to prevent bloodstream infections after TJA [46]. However, there is limited data to support this recommendation, and according to the latest American Academy of Orthopaedic Surgeons and American Dental Association guidelines, antibiotic prophylaxis following dental surgery in patients with a TJA is not universally indicated [51•]. Despite these recommendations, there remains ongoing debate on the appropriate role of antibiotics before dental procedures in patients with a TJA, and many providers continue to provide antibiotic prophylaxis in this setting to patients who are immunosuppressed due to underlying disease or medications.

Smoking

Smoking has been identified not only as a risk factor for the development of RA, but as a significant risk factor for prosthetic joint infection, and cessation should be addressed prior to surgery [52, 53]. Although the length of cessation has little scientific support, patients are generally counseled to stop smoking 4 to 6 weeks prior to surgery [54•, 55].

When Are Stress Doses of Glucocorticoids Indicated?

Glucocorticoids are used to manage both disease activity and flares in patients with RA and other inflammatory arthropathies [16••, 56, 57]. Traditionally, supra-physiologic “stress-dose” steroids were given to manage hemodynamic instability and adrenal insufficiency following the cessation of daily corticosteroid usage. Older literature focuses on administering a single dose of 100 mg of hydrocortisone intraoperatively for unilateral

arthroplasty procedures [46]. For bilateral procedures, hydrocortisone 100 mg could be given intraoperatively, followed by additional dosing every 8 h for 24 h, and a taper over the subsequent 24 h until the preoperative dose is met [46]. However, recent literature which reflects advances in anesthesia and surgical technique supports administration of the patient's daily dose of glucocorticoid instead of giving stress doses due to the higher risk of infection associated with high perioperative stress doses [16••, 46, 56]. Continuing home doses of steroids perioperatively specifically refers to adult patients who are taking less than 16 mg per day with a diagnosis of RA, ankylosing spondylitis, or psoriatic arthritis and not to patients with juvenile idiopathic arthritis [16••]. Such recommendations do not apply to patients with juvenile idiopathic arthritis or those who are being treated for hypothyroidism or primary adrenal insufficiency [16••]. It is recommended that patients receive a cumulative daily steroid dose of less than 20 mg per day to reduce the risk of infection. Preoperative adrenal function testing is generally not recommended because it correlates poorly to a patient's clinical course [16••, 46].

Diagnosing and Treating PJI in the Patient with Rheumatologic Comorbidities

Establishing a diagnosis of PJI is challenging, with patient comorbidities, duration of symptoms, and antibiotic use being some of the factors that can affect the clinical presentation. Furthermore, despite an increasing number of available PJI diagnostic tests, no gold standard method of diagnosis currently exists. In an effort to develop a standardized definition of PJI, the Musculoskeletal Infection Society (MSIS) convened a workgroup in 2011 and determined the presence of either one of two major criteria, or three or more minor criteria would indicate PJI (Table 2) [58]. Threshold values for serologic and synovial tests that may indicate acute or chronic PJI have been determined from literature review and consensus (Table 2). However, very limited data exists supporting such thresholds in diagnosing PJI in patients with coexisting inflammatory comorbidities.

The Role of Serum Inflammatory Markers CRP and ESR

Although C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be useful adjuncts to the diagnosis of PJI in this population, they can vary significantly in the context of active inflammatory disease. Thresholds of CRP > 1 mg/dL and ESR > 30 mm/h at a minimum of 3 weeks postoperatively were found to have inconsistent sensitivities and specificities in numerous studies in patients with inflammatory joint disease [59-62]. When comparing the two, CRP was noted to be the more sensitive measure of identifying PJI, when comparing to a gold standard PJI definition of one positive intraoperative culture with a virulent organism (streptococcus species or gramnegative bacterium) or three positive intraoperative cultures for less virulent organisms (coagulase-negative staphylococcus or *Propionibacterium*) [62]. Nevertheless, the American Academy of Orthopaedic Surgeons' published algorithm for diagnosing PJI in immunosuppressed patients, specifically including those on antirheumatic medications, notes that a positive ESR/CRP should prompt consideration of a joint aspiration for further evaluation [63]. While several studies have examined optimal serum ESR and CRP threshold values for diagnosing PJI, patients with inflammatory arthritis have been generally excluded from these analyses [61, 64]. In the

presence of limited data for patients with inflammatory arthritis, the current recommendations are to use the same threshold values for the diagnosis of PJI in all patients: CRP >100 mg/L within 6 weeks of surgery (acute PJI), and ESR > 30 mm/h, and CRP >10 mg/L for tests obtained more than 6 weeks from the most recent surgery (chronic PJI). It should be noted that ESR is thought to be unhelpful in the diagnosis of acute PJI [65••]. Further research on optimal ESR and CRP thresholds in predicting both acute and chronic PJI in the setting of underlying rheumatologic disease activity and antirheumatic medication use would be of clinical benefit.

Synovial White Blood Cell Count and Differential

Similar to serum ESR and CRP, the sensitivity and specificity of synovial fluid cell counts vary considerably due to the presence of underlying inflammatory arthritis [17]. However, while inflammatory synovitis may elevate synovial fluid white blood cell (WBC) counts and polymorphic neutrophil percentage (PMN%), these values have still been shown to be the most predictive of currently available tests in separating PJI from aseptic failure in patients with inflammatory arthritis [66]. In this light, positive inflammatory markers and a positive synovial fluid cell count, while still possibly secondary to inflammatory arthritis, should warrant further evaluation for PJI. Current recommendations for threshold values for synovial white blood cell counts and PMN% for the diagnosis of PJI are synovial WBC count > 10,000 cells/uL and PMN% > 90% within the first 6 weeks of surgery (acute PJI) and synovial WBC count > 3000 cells/uL and PMN% > 80% more than 6 weeks from surgery (chronic PJI) [65••].

Conclusion

Patients with inflammatory arthritis have a higher risk of PJI after TJA; however, there are several preventive, diagnostic, and therapeutic factors that can be optimized to lower the burden of PJI in this population. Specifically, this review presents and briefly discusses the current guidelines and evidence regarding risk reduction strategies in this high-risk population, as related to preoperative testing, medical optimization, perioperative medication management, and surgical planning. Considerations regarding PJI diagnosis in this population are also discussed. While certain PJI risk factors in this population are non-modifiable, such as a DMARD requirement to prevent frequent and severe inflammatory flare-ups, awareness of how to optimize these risk factors in the perioperative period is critical to properly allocate risk stratification and to counsel patients of their overall complication risk profile.

Although ample research efforts have been devoted to PJI following TJA, data pertaining to PJI in inflammatory arthritis patients undergoing TJA remains surprisingly limited. As such, best practices are sometimes determined from combining the latest evidence with multidisciplinary expert opinion. Future investigations studying PJI in this high-risk group are needed. Nevertheless, the evolution of clinical practice guidelines, advent of novel diagnostic tests looking at immune markers such as alpha-defensin, standardization of aspiration methods, and standardization of culture protocols to reduce variation may together

have large effects in improving the rates of PJI prevention and diagnosis in TJA patients with inflammatory arthritis.

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Table 1

Perioperative management of antirheumatic medications [15]

DMARDs (continue through surgery)	Dosing cycle	
Methotrexate	Weekly	
Sulfasalazine	Daily or twice daily	
Hydroxycholorquine	Daily or twice daily	
Leflunomide	Daily	
Doxycycline	Daily	
Biologic agents (stop prior to surgery, schedule surgery at end of dosing cycle)		
Adalimumab (Humira)	Weekly or every other week	
Etanercept (Enbrel)	Weekly or twice weekly	
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	
Infliximab (Remicade)	Every 4, 6, or 8 weeks	
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	
Certolizumab (Cimzia)	Every 2 or 4 weeks	
Rituximab (Rituxan)	2 doses 2 weeks apart every 4–6 months	
Tocilizumab (Actemra)	Weekly (SQ) or every 4 weeks (IV)	
Anakinra (Kineret)	Daily	
Secukinumab (Cosentyx)	Every 4 weeks	
Ustekinumab (Stelara)	Every 12 weeks	
Belimumab (Benlysta)	Every 4 weeks	
Tofacitinib (Xeljanz)	Daily or twice daily	*Stop 7 days before surgery

DMARDs disease-modifying antirheumatic medications

Table 2

MSIS definition for PJI and threshold values for minor criteria [58]

	Periprosthetic joint infection is defined as:
Major criteria	Two periprosthetic cultures with identical organisms or A sinus tract communicating with the joint or
Minor criteria	Three of the following five minor criteria - Elevated CRP and ESR - Elevated synovial WBC count or positive luekocyte esteraste test trip (synovial fluid) - Elevated synovial fluid PMN% - Positive histological analysis of periprosthetic tissue - A single positive culture
Threshold values	Acute PJI (< 6 weeks from surgery): CRP > 100 mg/L, ESR not useful, synovial WBC > 10 k cells/uL, PMN% > 90% Chronic PJI (> 6 weeks from surgery): CRP >10 mg/L, ESR > 30 mm/h, synovial WBC > 3 k cells per uL, PMN% > 80%