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Preoperative optimization to prevent periprosthetic joint infection in at-risk patients

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Abstract

Periprosthetic joint infection (PJI) remains an important complication with devastating consequences after total joint arthroplasties. With the increasing number of arthroplasties worldwide, the number of PJI will increase correspondingly with a significant economic burden to our healthcare system. It is likely impossible to completely eradicate PJI; hence, assessment and optimization of its risk factors to preventing such a disastrous complication will be the key. There are many strategies to prevent PJI in the preoperative, intraoperative, or postoperative phases. The preoperative assessment provides a unique opportunity to screen and diagnose underlying comorbidities and optimize modifiable risk factors before elective surgeries. In this review, we will focus on current literature in preoperative assessment of various modifiable risk factors and share the experience and practical approach in our institution in preoperative optimization to reduce PJI in total joint arthroplasties.

Keywords

joint replacements, periprosthetic joint infection, preoperative optimization, total joint arthroplasty

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Introduction

Despite advances in total joint arthroplasty, periprosthetic joint infection (PJI) remains an important complication with devastating consequences. Incidence of PJI ranges from 0.2% to 3% in the literature published over the last 10 years[1,2] and is the leading cause of revision arthroplasties, carrying significant morbidity, mortality, and healthcare expenses.[3–5] With the increasing number of arthroplasties performed all across the world, the number of PJI is expected to increase correspondingly. As it is likely impossible to completely eradicate the possibility of PJI, hence a better understanding and optimization of various risk factors will be the key to preventing such a disastrous complication.

Strategies to prevent PJI can involve preoperative, intraoperative, or postoperative phase. Preoperative measures are utmost important as it is the first line of defense. The preoperative assessment provides a unique opportunity to identify high-risk individuals and optimizes modifiable risks before proceeding to elective arthroplasties. Although demographic risk factors are largely nonmodifiable, apprehending them allows a better expectation of individual risk and enhances patient communication during informed consent.

Various modifiable risk factors for PJI had been identified and gained research interest.[6] Recent meta-analyses have reported that rheumatologic disease, obesity,

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hypoalbuminemia, preoperative anemia, diabetes mellitus, smoking, alcohol abuse, and history of steroid administration are significant modifiable risks for PJI.[2,7–9] While female gender and older age are nonmodifiable factors that appear to have a protective effect on PJI in recent systematic reviews and meta-analyses.[2,8]

In this review, we will focus on preoperative assessment and optimization of modifiable risk factors for PJI. Moreover, we will share our experience and practical approach in our institution in dealing with various risk factors before total joint arthroplasty. We will focus on patients at-risk of PJI instead of detailing general measures, such as perioperative antibiotic prophylaxis, the role of local infiltrative analgesia, and wound management.

Rheumatologic diseases

Numerous studies have shown an association between PJI and inflammatory joint diseases, such as rheumatoid arthritis (RA), juvenile inflammatory arthritis, ankylosing spondylitis, and psoriatic arthritis.[3,7,10,11] A review of 2543 primary total knee arthroplasties (TKA) found that the PJI rate in RA was 3.1%, which was significantly higher than 1.2% in non-RA patients.[12]

The reason for the increased risk in rheumatoid patients has several folds. Firstly, they are commonly on immunosuppressive medications which delay wound healing and impair immune responses. Moreover, associated skin lesions, anemia from chronic disease, and malnutrition further contribute to their increased risk of PJI.[10] A study investigating PJI in RA patients found that those using prednisolone greater than 15 mg/day, underweight (body mass index (BMI) < 18.5 kg/m^2) and coexisting coronary artery disease are significant risk factors in RA patients.[13]

Perioperative management of inflammatory joint disease medications is a delicate balance between the risk of wound healing, infection, and arthritis flare. Although level one evidence is limited, the American College of Rheumatology and the American Association of Hip and Knee Surgeons developed a guideline from expert opinions and consensus.[14] The guidelines suggest to continue nonbiologic disease-modifying antirheumatic drugs (DMARDs), including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and doxycycline, while biologic DMARDs should be stopped for one dosing cycle before elective total joint arthroplasty and restart after wound healing postoperatively (typically 2 weeks after surgery). Moreover, it recommends a continuation of the usual dose of corticosteroids rather than administering an additional 'stress-dose'.[14] A systematic review by Loza included four studies and concluded the continuation of low-dose methotrexate is safe during the perioperative period in RA patients.[15] However, the dose of methotrexate in the included studies varies from 5 to 10 mg/week and a prospective cohort observed four infections in the methotrexate group, while none in the control group.[15] Therefore, it would be wise to assess the condition of each RA patient individually and pay extra caution if decided to continue a higher dose of methotrexate perioperatively.

Although the diagnosis of rheumatoid disease is not modifiable, the antirheumatic medications should be adjusted and disease activity should be controlled before joint arthroplasties. Disease activity can be evaluated with composite scores, such as disease activity score-28 (DAS-28), simple disease activity index (SDAI), and clinical disease activity index.[16] DAS-28 and SDAI include blood testing for C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). It is important to avoid surgery during RA flares to reduce the risk of PJI. In our institute, we would refer rheumatoid patients with persistently elevated ESR or CRP to a rheumatologist for further assessment, including ultrasound examination for subclinical synovitis, and treat accordingly.

Diabetes mellitus

Diabetes mellitus has been associated with increased risk of PJI and wound complications in various studies.[7,17–19] The odd ratio for surgical site infection and wound complications ranges from 1.19 to 3.75.[7,17–19] Besides, uncontrolled diabetes has a higher risk of stroke, urinary tract infection, ileus, transfusion, and even death.[18] Unfortunately, the incidence of diabetes is increasing[20] and it is reported that 22% of patients undergoing TKA are diabetic.[19] Our institute performs universal hemoglobin A1c (HbA1c) screening for all arthroplasty patients and our local data found that 66% of patients scheduled for TKA are either diabetic or prediabetic, while 39% have undiagnosed diabetes or prediabetes before surgery. Our findings were consistent with a recent study in the United States, where 33.6% had undiagnosed dysglycemia.[21]

Different glycemic markers and their thresholds to predict PJI had gain lots of research interest. HbA1c and perioperative glucose levels are the most extensively studied glycemic markers. A systematic review and meta-analysis in 2017 supported the association of high HbA1c and perioperative hyperglycemia with PJI after joint arthroplasty.[22] Cancienne et al. studied 17,435 diabetic patients and found that the PJI increases with HbA1c and proposed a cutoff of 8 mg/dL.[23] Another retrospective review by Tarabichi et al. found that PJI was the only complication associated with a high HbA1c and proposed a threshold of 7.7%.[24] Recent meta-analyses by Shohat et al., included 10 studies, found that elevated HbA1c associates with a higher risk of infection after total joint arthroplasty (TJA); however, there was a significant heterogeneity between the studies (I^2 = 81.32%, $p < 0.001$), and subgroup analysis found no association between HbA1c greater than 7% and PJI.[25] Although elevated HbA1c should be optimized, HbA1c alone is not sensitive and reliable enough as a predictor of PJI.

Postoperative blood glucose is another glycemic marker that was shown to associate with PJI. Kheir et al. reviewed more than 20,000 arthroplasty patients and found that the PJI increases with day 1 fasting glucose with a threshold of 137 mg/dL, regardless of the patient's diabetic status.[26] This finding was consistent with previous studies by Reategui and Mraovic, where higher day 1 fasting glucose was associated with an increased risk of infection.[27,28] Most studies reported the morning fasting glucose on postoperative day 1. Varady examined the optimal timing of glucose measurements and found that hyperglycemia was more common on the night of surgery in both diabetes and non-diabetes.[29] Moreover, Shohat et al. suggested that glycemic variability is an important parameter associated with PJI and mortality after total joint arthroplasty.[30] Further studies, such as continuous glucose monitoring, will be necessary to characterize postoperative glucose profile in arthroplasty patients.

Fructosamine was proposed in recent studies to be a better glycemic marker in predicting PJI after TKA. HbA1c is a marker of glycemic control over the past 3 months, while fructosamine reflects on glycated serum proteins, which has a half-life of 2–3 weeks. As a result, fructosamine levels are more representative of short-term variation in glucose control. A prospective multicenter study involving 1119 patients found that patients with high fructosamine levels were at a much higher risk of PJI, readmission, and reoperation at 3 months from surgery.[31] A fructosamine level of 293 μmol/L was proposed as a cutoff for postoperative complications.[31] More research is required to ascertain the role of the different glycemic markers and their thresholds in predicting PJI.

In our institution, the preoperative assessment includes universal HbA1c screening for all TJA patients, regardless of their diabetes status. We also started on fructosamine screening recently given the latest evidence.[31,32] If the HbA1c result is greater than 7.5%, the patient will be referred to an endocrinologist for further optimization before proceeding to surgery. From our local experience, our data showed that preoperative HbA1c screening and optimization reduces the PJI rate in TKA patients when compared with historical control without universal HbA1c screening.

Anemia

Anemia is another risk factor for PJI with an adjusted hazard ratio of 1.36 and 1.26 for total hip and knee arthroplasty, respectively.[19,33] Greenky et al. reviewed more than 15,000 total hip and knee arthroplasties and found that 19.6% have preoperative anemia and 44% required blood transfusion postoperatively.[34] Compared with non-anemic patients, preoperative anemia significantly increased the risk of PJI, length of stay, and mortality.[34]

Optimization of preoperative anemia is important to reduce blood transfusion and PJI. During the preoperative assessment, the underlying cause of anemia should be investigated and provide appropriate treatments. Options to optimize preoperative anemia include the use of recombinant human erythropoietin and autologous red blood cell transfusion.

In our institute, we follow the concept of patient blood management and started a multidisciplinary program since 2014.[35] There are three pillars of patient blood management in reducing blood transfusion, including preoperative hemoglobin optimization, minimize perioperative blood loss, and improve physiological tolerance to anemia.[35] We perform preoperative anemia screening and collaborate with the hematologist for further investigations and optimizations.[36] For instance, patients suffering from iron-deficiency anemia will have further workup for any gastrointestinal blood loss and given iron supplements to optimize their hemoglobin level before surgery. Combined intravenous and intra-articular tranexamic acid is routinely given to reduce intraoperative blood loss unless contraindicated, such as a history of cerebrovascular disease or transient ischemic attack, ischemic heart disease, acquired on congenital coagulopathy or prior thromboembolic disease.[37] Moreover, active warming during the surgery was implemented to prevent hypothermia. Intraoperative hypothermia is associated with greater blood loss and need for transfusion.[38,39] Finally, we employed a restrictive transfusion policy with a stringent transfusion trigger and a single unit transfusion.[36] Our local data showed that the transfusion rate was significantly reduced after the implementation of the patient blood management program with no difference in the readmission rate.[36]

Obesity

Obesity is associated with osteoarthritis and hence it is a commonly encountered condition during preoperative assessment for total joint arthroplasty. Overweight, obesity, and morbid obesity are defined according to the BMI greater than 25 kg/m^2, 30 kg/m^2, and 40 kg/m^2, respectively.[40] World Health Organization (WHO) concluded that Asians had a substantial risk of type 2 diabetes and cardiovascular disease at lower BMI than the existing cutoff for overweight or obesity.[41] Instead of redefining the BMI thresholds for individual populations, WHO suggested trigger points for public health intervention at BMI greater than 23 and 27.5 kg/m^2.[41]

Obesity is associated with a longer operation time, more postoperative complications, and higher revision rates.[42,43] It was shown by multiple studies that obesity increases the risk of PJI with odds ratios between 1.73 to 6.4.[33,44,45] Malinzak reviewed more than 6000 total joint arthroplasties and found the odds of PJI is 3.2 and 18.3 times in morbidly obese and extreme obesity patients (BMI greater 50 kg/m^2).[46]

Despite being a modifiable risk factor, preoperative weight loss was reported to have no effect on surgical site

infection and readmission rates after arthroplasties.[47] Bariatric had been suggested as a way to optimize morbidly obese patients before total joint arthroplasties, however, such practice remains controversial. A recent meta-analysis of more than 38,000 patients shown that prior bariatric surgery was associated with better short-term outcomes, but no effect on wound infection and long-term risk of PJI, dislocation, fracture, and revisions.[48] Springer et al. followed-up 289 morbidly obese patients with end-stage osteoarthritis and found that only 20% eventually received joint arthroplasty and less than 40% were able to lower their BMI to less than 40 kg/m^2 at the time of surgery.[49] Therefore, withholding surgery and hoping to incentivize weight loss might not be a realistic approach. Although it remains controversial on the best way to optimize obesity, enhancing patient education and communication together with a collaborative approach should better encourage weight control in morbidly obese patients.

Malnutrition

Malnutrition reduced the body's ability to synthesis collagen and impair its immune response, thus affects a patient's wound healing and ability to fight infections.[50] Malnutrition is diagnosed by various laboratory markers, such as serum transferrin less than 200 mg/dL, serum albumin less than 3.5 g/dL, and total lymphocyte count less than 1500 cells/mm^3.[50,51] Preoperative low albumin was suggested, among other malnutrition markers, to have high specificity and positive predictive value for PJI.[52]

Multiple studies have reported malnutrition is associated with an increased risk of adverse outcomes after total joint arthroplasties, including PJI and readmissions.[52,53] Huang prospectively followed 2161 arthroplasty patients and found that malnourished patients had a significantly higher rate of overall complications (12% vs. 2.9%), including hematoma formation and PJI than patients with normal laboratory parameters.[54] In Huang's cohort, the incidence of malnutrition was 8.5%, while 42.9% had coexisting obesity.[54] Malnutrition can also coexist with obesity, where patients have high caloric but nutritionally poor diets, so-called paradoxical malnutrition. A recent meta-analysis included more than 250,000 patients found the odds ratio of PJI in malnourished patients after total knee and total hip arthroplasty were 2.55 and 3.1 respectively.[55] The risk of PJI was higher in both primary and revision total joint arthroplasties in malnourished patients.[55]

A prospective study by Schroer et al. supported that nutritional intervention in malnourished patients can improve the outcome of total joint arthroplasties.[56] The cohort that offers high protein, anti-inflammatory diet to patients with low serum albumin had a shorter length of stay, and lower hospital charges compared with controls.[56] This provides evidence that preoperative screening of laboratory markers and dietary intervention is important. Malnourished patients should be referred to a dietician for nutritional supplements before total joint arthroplasties. Moreover, we should look out for other associated conditions with malnutrition, such as alcoholism, smoking, gastrointestinal tract pathology, and obesity.

Vitamin D deficiency

Vitamin D deficiency, defined by serum 25-hydroxyvitamin D less than 20 ng/mL, is unfortunately quite common with a prevalence of 41.6% in the United States and ranges from 13% to 80% in patients with knee or hip arthroplasties.[57–60] Besides being a key player in bone metabolism, vitamin D also has a role in neutrophil motility, macrophage activity, and immune modulation.[61,62] Vitamin D deficiency is associated with poorer postoperative outcomes after arthroplasty.[60,63] Moreover, vitamin D deficiencies are more common among patients with PJI than in primary arthroplasty and revision for aseptic loosening.[64] Hedge et al. reported an odds ratio of 1.76 and 2.97 for PJI requiring irrigation and debridement, and prosthesis removal within 1 year after TKA in vitamin D deficient patients.[60]

A mouse model of PJI has shown that vitamin D deficiency increases the bacterial burden and neutrophil infiltration, while preoperative repletion of vitamin D can reverse its effect.[65] Although up till now no clinical study demonstrates the correction of vitamin D deficiency can reduce PJI, a cost estimation predictive model by Arshi et al. supports the role of vitamin D repletion.[66] In their model, nonselective vitamin D repletion was more cost-effective than selective preoperative screening and repletion due to the low cost of vitamin D repletion relative to laboratory testing.[66]

More high-quality clinical studies would be required to further delineate the role of vitamin D screening and repletion on outcomes after arthroplasties. We suggest selective checking of vitamin D levels in high-risk patients and provide supplements preoperatively if deficient.

Prior intra-articular injections

Intra-articular steroid or viscosupplements are frequently offered to patients with osteoarthritis of the knees that failed conservative treatment. Up to 30% of TKA patients had prior intra-articular steroid injections.[67] Whether prior intra-articular injection is a risk factor for PJI is still controversial with conflicting results in the literature.

Two meta-analyses were published in 2014 and concluded that prior intra-articular steroid injection did not increase the risk of PJI.[68,69] On the other hand, Cancienne et al. reviewed more than 35,000 TKA patients and showed that intra-articular steroid injections within 3 months before surgery significantly increase the risk of PJI, while no difference if the injection was more than 3 months ago.[70] Another retrospective review in 2017 included more than 29,000 TKA with prior corticosteroid or hyaluronic acid

injections and 54,000 controls found a time-dependent risk of PJI with significantly higher risk if the injections were within 6 months before TKA.[71]

Because of a possible increase in risk of PJI with prior intra-articular injections, we suggest to avoid any injections within 6 months before TKA or delay TKA to more than 6 months after the injections.

Staphylococcus aureus nasal carrier

The reported incidence of methicillin-sensitive (MSSA) and resistant *Staphylococcus aureus* (MRSA) nasal colonization in arthroplasty patients are 22% and 0.8%, respectively.[72] *S. aureus* colonizers have increased risk of staphylococcal infection after total joint arthroplasties, which are molecularly identical to those isolated in their nares.[73,74] Studies are showing routine MRSA and MSSA screening and decolonization can reduce PJI.[75,76] Sporer et al. reported that selective treatment of screened positive patients with intranasal mupirocin and chlorhexidine gluconate showers for 5 days can decrease surgical site infection by 69%, from 1.11% to 0.34% in their cohort.[76] Moroski evaluated the current decolonization protocol and found that although it is effective, there are still 5.2% of patients with MSSA and 0.35% with MRSA positive culture on the day of surgery.[77]

International Consensus Meeting on Periprosthetic Joint Infection in 2013 acknowledged MSSA and MRSA screening and decolonization can reduce the incidence of PJI, however, the workgroup did not recommend universal screening for all arthroplasty patients, as we are not sure about the cost-effectiveness of routine screening.[78] The cost of routine *S. aureus* screening and decolonization are high and there are concerns of developing resistant bacteria strains with the widespread use of topical antibiotics. Therefore, selective screening to high-risk patients or healthcare workers should be considered.

Urine screening

Screening for bacteriuria before total joint arthroplasty remains a controversial topic. International Consensus Meeting on Orthopaedic Infection in 2018 did not recommend routine preoperative urinary screening, while symptomatic urinary tract infection should be treated with antibiotics before total joint arthroplasty.[79]

Recent studies also found that asymptomatic bacteriuria has no causation relationship with PJI. Weale et al. performed a retrospective review of more than 4000 arthroplasty patients.[80] Although they found a higher PJI rate in patients with asymptomatic bacteriuria, most bacteriology did not match.[80] A meta-analysis by Gomez-Ochoa included more than 2000 total joint arthroplasty patients in 11 studies found no difference in the PJI rate between treated and untreated bacteriuria.[81] Hence, there is limited evidence to support preoperative screening and treatment of asymptomatic bacteriuria.

Dental screening

Poor oral hygiene causes transient bacteremia during daily activities, such as tooth brushing, flossing, and chewing, which in theory increases the risk of hematogenous seeding of bacteria and PJI.[82] The incidence of untreated dental pathology in arthroplasty population was reported to be 23%.[83] However, limited evidence demonstrating the relationship between preoperative dental clearance and PJI. A recent retrospective review by Sonn et al. found that preoperative dental evaluation and extraction did not affect complications or the rate of PJI after total joint arthroplasties.[84] Furthermore, the International Consensus Meeting on Orthopaedic Infection in 2018 recognized the risk of hematogenous spread of oral pathogens in patients with poor oral hygiene and support patients with oral disease, and dentition should be optimized before arthroplasty.[79] However, due to limited evidence and the lack of prospective controlled studies, the workgroup in the International Consensus Meeting in 2018 did not support routine dental clearance before surgery.[79]

Conclusion

Preoperative assessment before elective arthroplasty provides an excellent opportunity to detect and optimize various risk factors for PJI. Despite our understanding of PJI and its risk factors, it will remain as an important challenge to arthroplasty surgeons and patients.

Prevention will be the key to tackle this challenging complication. Preoperative evidence-based driven protocol should be implemented to maximize our patient's safety and benefit in undergoing arthroplasties.

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