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Periprosthetic Knee Infection: Ten Strategies That Work

Javad Parvizi, MD, Priscilla Ku Cavanaugh, MS, and Claudio Diaz-Ledezma, MD
Department of Orthopaedic Surgery, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Periprosthetic joint infection (PJI) is one of the most serious complications following total knee arthroplasty (TKA). The demand for TKA is rapidly increasing, resulting in a subsequent increase in infections involving knee prosthesis. Despite the existence of common management practices, the best approach for several aspects in the management of periprosthetic knee infection remains controversial. This review examines the current understanding in the management of the following aspects of PJI: preoperative risk stratification, preoperative antibiotics, preoperative skin preparation, outpatient diagnosis, assessing for infection in revision cases, improving culture utility, irrigation and debridement, one and two-stage revision, and patient prognostic information. Moreover, ten strategies for the management of periprosthetic knee infection based on available literature, and experience of the authors were reviewed.

Keywords: **Knee, Arthroplasty, Periprosthetic joint infection, Infection control, Reoperation**

Introduction

It is well recognized that a periprosthetic joint infection (PJI) after knee arthroplasty is a catastrophic complication not only for the patient, but also for the health-care system. During the last decade, clinical research has considerably improved our comprehension of this topic. However, we are still in the process of producing high-level evidence to support our daily clinical practice. In this article we will review ten strategies that work in managing knee PJI.

1. Preoperative Risk Stratification

From our standpoint, the first step to succeed in the battle against knee PJI is prevention. Consequently, in order to stratify the patient's risk, knowledge of risk factors in the development of PJI should be mandatory for each surgeon that is involved in knee arthroplasty. Optimization of modifiable variables that may influence this risk is also critical. A recent study by Namba et al.[1] evaluated 56,216 total knee arthroplasty (TKA) surgeries. The study found an incidence of deep infection of 0.72% (404/56,216). The risk factors for infection were body mass index (BMI) of ≥35 (hazard ratio [HR], 1.47), diabetes mellitus (HR, 1.28), male sex (HR, 1.89), an American Society of Anesthesiologists (ASA) score of ≥3 (HR, 1.65), osteonecrosis (HR, 3.65), and posttraumatic arthritis (HR, 3.23). Hispanic race was a protective factor (HR, 0.69), the use of antibiotic irrigation (HR, 0.67), a bilateral procedure (HR, 0.51), and a lower annual hospital volume (HR, 0.33). Surgical risk factors included quadriceps-release exposure (HR, 4.76), and the use of antibiotic-laden cement (HR, 1.53). Operative time was a risk factor, with a 9% increased risk per fifteen-minute increments. Although some risk factors found in this study are debatable, the study highlights some of the important predisposing factors for infection.

Obesity and diabetes are both well-known risk factors for knee PJI. According to the American Association of Hip and Knee Surgeons (AAHKS), prior to surgery, a patient with a BMI over 40 should be counseled regarding weight loss[2]. In addition, AAHKS has emphasized the importance of a nutritional evaluation prior to surgery[2]. Regarding diabetes, a large Finnish study corroborated its relevance as a strong risk factor for infections[3]. Although Hemoglobin A1C has been used to evaluate arthro-

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Correspondence to: Javad Parvizi, MD
Department of Orthopaedic Surgery, Thomas Jefferson University Hospital, 111 S 11th St, Philadelphia, PA 19107, USA
Tel: +1-267-339-7813, Fax: +1-215-503-5651
E-mail: parvj@aol.com

plasty patients, a recent publication from Iorio et al.[4] showed that it is probably a suboptimal preoperative measurement due to its inability to prognosticate complications. We believe that an exhaustive preoperative evaluation, and glycemic level optimization is an indispensable component of the preoperative work up, and must be conducted by a general internist, or medicine subspecialist. Currently, the evidence is not able to present a definite threshold regarding BMI and glycemic control in order to establish a clear preoperative recommendation for knee arthroplasty patients.

Another attractive strategy is to calculate a preoperative risk of PJI using a scoring system. The Mayo Clinic recently presented a prosthetic joint infection risk score, which demonstrated a good capacity to discriminate subjects who will develop a PJI from those who will not (C-index of 0.722)[5]. It includes the BMI, presence of prior operations on the index joint, prior arthroplasty, immunosuppression, ASA score, and procedure duration[5]. After adding postoperative wound drainage to the previous variables, the 1-month post surgery risk score presents a C- index of 0.716.

A recent study conducted in Korea described a prevalence of surgical site infections (SSI) in 161 of 6,848 cases (2.35%)[6]. Interestingly, the authors suggested that the risk factors for SSI differ between total hip arthroplasty (THA), and TKA. Independent risk factors for SSI in TKA were male gender, and an operating room without laminar flow. More than 10 procedures per month was a protective factor for knee PJI[6].

A recent systematic review and meta-analysis indicate that, compared with osteoarthritis (OA) patients, patients with rheumatoid arthritis have a higher risk of infection following TKA[7].

Another important risk factor is revision surgical procedures[8]. A study from our institution revealed that the risk of infection among patients undergoing revisions was 10-fold higher (9%)[8] than for patients undergoing primary TKA (0.5%–1%)[9]. The risk was predicted by factors such as revision due to infection, higher Charlson comorbidity index, and diagnosis other than OA at the time of the primary procedure.

Understanding the risk factors for PJI, allows implementation of strategies that aims to reverse some of these potential risk factors and reduce the burden of infection.

2. Preoperative Antibiotics

One of the most effective strategies for the prevention of infection in modern orthopaedic literature is the administration of preoperative antibiotics[10,11]. In order to achieve optimal results, adequate concentration of antibiotics should be present during the entire time the incision is open, when the greatest risk for contamination is present[10]. For predictable and rapid delivery of antibiotics, systematic intravenous (IV) administration is the method of choice[12].

Conflicting opinions exist as to what the optimal time window for prophylaxis administration should be[12]. Some studies have shown that the best time for administration is within 30 minutes of incision[13], while others support administration within 30–59 minutes[14]. Based on The American Academy of Orthopaedic Surgeons (AAOS) and The Centers for Disease Control (CDC) guidelines, prophylactic antibiotics should be administered within one hour before the surgical incision[15]. When a proximal tourniquet is used, administration of the entire dose of antibiotic should occur before inflation of the tourniquet[12,15]. Duration of antibiotic coverage should not exceed 24 hours postoperatively[15], doing so may increase the risk for adverse effects of antibiotics without proven benefits[15,16]. Avoiding unnecessary antibiotic use will also minimize the risk ofbacterial resistance[17]. Furthermore, intraoperative dose of antibiotic should be repeated if there is significant blood loss, or if operative time exceeds two times the half-life of antibiotic[15,18].

Currently, the most widely used prophylactic antibiotics for prevention of PJI are first and second generation cephalosporins because of their excellent tissue penetration, bioavailability, and coverage against common organisms such as *Staphylococcus* species, and enteric pathogens[12]. In patients undergoing orthopaedic procedures, cefuroxamine and cefazolin are the preferred antibiotics[14]. These antibiotics may not be appropriate in certain cases, and the addition of vancomycin may be warranted[12,15]. AAOS guidelines recommend vancomycin in facilities with methicillin-resistant staphylococcus aureus (MRSA) outbreaks, and in patients with known MRSA colonization[15]. Additionally, vancomycin should be considered in institutionalized patients (dialysis-dependent patients and nursing home residents), and health care workers[12]. Patients with a documented anaphylactic reaction to penicillin can either receive clindamycin or vancomycin[12,15], however, our institution prefers vancomycin to avoid the potential for clindamycin-associated *clostridium difficile* enteritis[12].

3. Skin Preparation

Preoperative skin preparation is of common practice in the orthopaedic community. Skin preparation prior to surgery includes skin decolonization, antisepsis, hand washing by the surgeon, and hair removal. Ample evidence exists in support of the role of preoperative cleansing in reduction of skin bacteria load[19,20], but how this translates to prevention of SSI is unclear.

Preoperative showering or cleansing with an antiseptic agent at

least the night before a surgical procedure has been recommended by the CDC[21]. In two prospective consecutive series, patients who used chlorhexidine gluconate (CHG) impregnated wipes the night before, and the morning of the surgery had a lower incidence of SSI as compared with those who did not comply to the protocol in both THA and TKA procedures. In contrast, a Cochrane review of 7 randomized trials concluded that preoperative showering with CHG did not reduce the rate of SSI as compared to a no shower group or placebo group[22]. Despite conflicting data regarding preoperative showers reducing SSI incidence, the simplicity and cost-effectiveness of this method justifies its current recommendation[23].

Regarding skin preoperative disinfection, the discussion has focused on the selection of an optimal antiseptic agent[12]. The main types of antiseptic agents are: alcohol based solutions, povidone-iodine and CHG[24,25]. In studies comparing CHG and povidone-iodine the results are conflicting. Darouiche et al.[26] demonstrated that CHG in alcohol was superior in reducing the rate of SSI as compared to aqueous povidone-iodine. However, the iodine preparation in the study did not use an alcohol solvent, hence allowing for the possibility that alcohol may play a role. In fact, in a study involving general surgery patients, povidone-iodine prepped patients had a lower rate of SSI when alcohol was used (either as a solvent or scrub)[27]. Overall, the literature suggests some value in the combination of alcohol with antiseptic agents, and that CHG combined with alcohol may be superior to other combinations[26,28,29].

In regards to preoperative hair removal, the CDC recommends that it should be done immediately before the procedure, and electric clippers are preferred over razor blades[12,21]. Tanner et al.[30] conducted a meta-analysis that showed that electric clippers were associated with fewer SSIs than with razor shaving.

Hand washing by the surgeon and medical personnel is a difficult topic to evaluate due to the variability in the literature regarding duration, and optimal antiseptic agent. One study examining surgical scrub time, and subsequent bacterial growth found no significant difference between a 2 or a 3 minute scrub[31]. Currently, The Association of Perioperative Registered Nurses states that a 3–4 minute scrub is as effective as a 5 minute scrub, while the CDC recommends 2–5 minutes[21]. Data on hand rub (alcohol based) and hand scrub agents suggest no significant difference in efficacy between the two[32]. A trial of 4,387 patients who underwent clean, and clean contaminated surgery using either traditional hand scrubbing techniques or waterless, alcohol-based antiseptics showed no difference in SSI rates[33]. Based on current literature, medical personnel should consider a minimum duration of 2–3 minutes for surgical hand antisepsis using either hand rub or hand scrub solution[31-33].

4. Diagnosis of Periprosthetic Joint Infection

The diagnosis of PJI should be suspected in all patients evaluated for a painful TKA. The AAOS established diagnostic guidelines that help identify PJI of the knee[34]. The measurement of serum markers such as C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) is highly valuable in reaching a diagnosis of PJI. It must be noted that these tests are not diagnostic independently. According to the AAOS[34] and the Infectious Diseases Society of America guidelines[35], if serum markers are elevated, a joint aspiration should be performed. Our institution always includes cytochemical fluid analysis, and two cultures after every knee aspiration. More recently, we have added the evaluation of the leukocyte esterase test also[36].

We encourage the surgeons to be cognizant of the Musculoskeletal Infection Society (MSIS) PJI diagnostic criteria, that aim to provide a standard definition of PJI[37]. The criteria can be used as a guide to establish a diagnosis when PJI is suspected. Taking into consideration the benefits, costs and risks of different strategies of PJI diagnosis, the use of serum markers followed by knee arthrocentesis is a highly efficient strategy.

A recent study from our group determined the thresholds for serum markers to diagnose PJI using the MSIS criteria. In early postoperative knee PJI, the ESR threshold was 54 mm/hour, and CRP was 23.5 mg/L. In late-chronic knee PJI the thresholds were 46.5 mm/hour for ESR, and 23.5 mg/L for CRP[38]. A study from another group established that the rate of false negatives was 9.2% for ESR, 5.3% for CRP, and 11% for combined ESR and CRP when diagnosing knee PJI. The authors believe that one of the factors that may explain these observations is that some patients may not mount a sufficient immune response, especially in early postoperative infections[39]. For this reason, a joint aspiration should be conducted even if serum markers are normal in those cases with high clinical suspicion, or known risk factors for knee PJI.

Our group also presented the value of studying the CRP in the synovial fluid, which may be an additional tool to improve our diagnostic alternatives[40].

5. Intraoperative Assessment in Every Revision Case

From our standpoint and according to the recommendations made by the AAOS, surgeons should always perform a PJI diagnostic workup in every revision case. This process should start when the decision to undergo a revision is made, and the strate-

gies described above are used. Once the patient is in the operation room, three main strategies can be employed: 1) cultures, 2) frozen sections, and 3) implant-related studies.

Concerning intraoperative cultures, one of the most important steps is to not withhold the preoperative antibiotics in revision cases. A multicenter randomized study, demonstrated that intraoperative cultures yielded the same organisms as preoperative cultures in 28 of 34 patients (82%) randomized to receive antibiotics before the skin incision compared to 25 of 31 patients (81%) randomized to receive antibiotics after obtaining operative cultures[41]. In regards to the type of cultures that should be obtained during the surgery, a study conducted in our institution demonstrated that tissue cultures are better than swab cultures. Tissue cultures demonstrated higher sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for diagnosing PJI than swab cultures. Swab cultures had more false-negative and false-positive results than tissue cultures[42] Another important strategy is to obtain the synovial fluid culture in blood culture flasks, due to its higher sensitivity, specificity, and both PPV and NPV for diagnosis of PJI when compared with standard tissue and swab samples[43].

Regarding the use of frozen sections, it must be noted that they represent one of the diagnostic criteria in the MSIS definition. A recent systematic review and meta-analysis by Tsaras et al.[44] showed that intraoperative frozen sections are helpful in the diagnosis of culture-positive PJI, but had moderate accuracy in ruling out this diagnosis. According to the authors, frozen section is especially valuable if the suspicion of infection remains high even after a negative preoperative evaluation. The optimum diagnostic threshold (number of polymorphonuclear leukocyte per high-power field) could not be discerned in this study.

Implant sonication is proving to be an interesting technology[45]. Its role has not been completely determined in the diagnostic work-up of PJI, especially considering the costs associated.

6. How to Improve the Utility of Cultures?

Cultures of tissue and synovial fluid obtained from an affected joint play a major role in both the diagnosis and treatment of PJI[12]. These cultures are used to confirm, and not to screen for PJI[12]. Currently, diagnosis of PJI can be made from two separate fluid or tissue samples from an affected joint[37]. Not only do cultures confirm a PJI diagnosis, they also allow for sensitivity-guided treatment. However, in 7% to 12% of PJI cases cultures may be negative even when clear signs of infection are present[46,47].

Negative cultures may be caused by a variety of reasons, including inappropriate collection of sample, use of antimicrobial therapy prior to collection, short incubation duration, and possible fungal or mycobacterial infection[12]. In the setting of a true PJI, negative cultures limit the ability to tailor antibiotic treatment and may hinder justification for revision surgery[12]. Thus, attention should be directed at decreasing the incidence of negative cultures.

Strategy for obtaining positive cultures includes withholding aspiration of joints for at least two weeks prior to sample collection, followed by a prolonged period of incubation[12,46]. A study by Schaefer et al.[48] described that prolonged incubation for at least 14 days increased the identification of organisms that would otherwise remain culture negative. Certain pathogens that are difficult to isolate using traditional cultures include fungi, mycobacteria, and organisms encapsulated in biofilm[46]. Proper media should be used in cases where fungi or mycobacteria are suspected[12]. A repeat aspiration should be considered in the event of inconclusive preoperative aspiration, negative cultures, elevated inflammatory markers, and high PJI suspicion[12].

7. Irrigation and Debridement: When and How?

The use of irrigation and debridement (I&D) with or without modular exchange as an appropriate alternative for treatment of PJI remains controversial. This less invasive procedure is commonly used despite its rate of success ranging between 0% and 89%[49]. I&D provides the option for a less complex surgery, and lower cost when compared to two-staged procedures[50]. The potential advantages of I&D over two-stage exchange justify its continued practice and further investigation of factors that predict its optimal use.

I&D has been considered a viable option for early postoperative or late hematogenous infections[51]. Previous studies have suggested that the ability of I&D to control infection may be related to its timing relative to index total joint arthroplasty, and duration of symptoms[52-54]. Hartman et al.[52] found significant improvement in I&D success rates if used within 4 weeks of index knee surgery. In addition to short duration of symptoms, the literature suggests a higher I&D success rate in healthier patients, and in infections with low virulent organisms[55-58]. Azzam et al.[59] described that patients with a higher ASA score, had higher failure rates. Furthermore, several studies recognize Staphylococcal infections as a risk factor for failure in I&D[60]. Thus, I&D should be considered in immunologically optimized patients with acute onset of symptoms infected with low virulent organisms.

Once the decision to perform an I&D procedure is made, preoperative optimization of the patient should be attempted before proceeding[12]. In the operating room, aggressive debridement

of all foreign and affected periarticular tissue should be performed[12]. At our institution, retained components are scrubbed with Dakin's solution and using a new, clean instrument for each collection, at least 3 tissue samples are then obtained[12]. Thorough irrigation using low pressure pulse lavage or bulb irrigation of the joint with up to 9 liters of solution is performed[12,61,62]. Finally, gloves, gowns and surgical setup should be changed between the I&D procedure, and the modular component exchange[12].

8. Revision in One Stage: When and How?

One-stage exchange arthroplasty for PJI has become the subject of interest due to potential advantages over two-stage exchange. Main advantages that proponents focus on are the need for a single operation, decreased morbidity, lower cost, and improved functional results[63-65]. Regarding efficacy of the procedure, several retrospective studies have reported rates of infection control between 73% and 93%[66-69].

Although advantages may exist in one-stage exchange, studies emphasize that success of the procedure depends on both patient, and infection related factors[12]. Jackson and Schmalzried[70] performed a literature review to determine when single-stage exchange is most successful in the setting of an infected hip. Variables associated with successful outcomes included the absence of wound complications after index THA, healthy patients, presence of methicillin-sensitive organisms, and organism susceptibility to antibiotic-laden bone cement[70]. Factors that predicted failure included polymicrobial infection, presence of gram negative organisms, and methicillin-resistant organisms[70]. Furthermore, the following may be considered contraindications: systemic infection, severe soft tissue involvement, inability to identify a microorganism preoperatively, and presence of a sinus tract[10,12,35,70-72]. Identifying ways to optimize results of one-stage exchange helps determine appropriate indications. At our institution, indications for one-stage exchange include: a healthy host, acute postoperative infection, susceptible organism, and adequate soft tissue coverage[12].

In one-stage exchange arthroplasty, a patient undergoes a radical synovectomy, debridement of infected tissue and removal of foreign material (including prosthesis and cement)[65]. Multiple cultures should be taken for final culture analysis[12]. Prior to the reimplantation of the prosthesis, the patient should be reprepped, and a change of gloves and surgical instruments should occur[65]. After implantation of the antibiotic impregnated cement, the wound is irrigated with dilute betadine solution before final closure[65]. Systemic antibiotics are usually given for a total of 6 weeks, beginning with 2 weeks of IV antibiotics followed by 4 weeks of oral antibiotics[65].

9. Revision in Two Stages: When and How?

The two-stage exchange arthroplasty is currently the most accepted procedure for the treatment of PJI in North America[73-75]. Two-stage exchange involves resection of the implants, meticulous debridement and irrigation, placement of a temporary antibiotic-impregnated cement spacer, and delayed component reimplantation[12,65]. Although the main role of two-stage revision has been in chronic PJI management, it is increasingly considered in cases of acute PJI where initial I&D or one-stage exchange procedures have failed[12,76]. Literature on two-stage exchange reports variable success rates, and sufficient data directly comparing it to one-stage revision is lacking. However, a recent systematic review demonstrated an average success rate of 90% after two-stage exchange for knee prosthesis infection[75]. The study also reported that two-stage exchange provided better outcomes than one-stage revision for septic knee prosthesis[75].

Currently, there is insufficient data to provide clear indications for two-stage exchange[35,70,72]. Infections with resistant organisms have been associated with higher failure rates in the treatment of PJI[77,78]. Some studies suggest that two-stage exchange may be the preferred treatment for highly virulent organisms[79,80]. Parvizi et al.[79] examined surgical treatment success of knee and hip MRSA infections, and reported infection control by I&D and two-stage exchange as 37% and 75% respectively, suggesting superior outcomes with the latter. Furthermore, Oussedik et al.[64] reported significant bone loss, and soft-tissue compromise as factors in favor of a two-stage exchange over a one-stage revision. Insufficient soft-tissue coverage may be an indication for two-stage exchange, especially if time is required for flap development. Currently at our institution, common indications for this procedure are as follows: chronic PJI, failed I&D, and acute infections associated with an immunocompromised host or virulent organism[12].

Two-stage exchange begins with thorough removal of infected tissue and foreign material, followed by irrigation[12]. The first stage involves insertion of either a static or dynamic antibiotic-impregnated spacer[12], most commonly using vancomycin, tobramycin, and gentamicin as the antibiotic[12,81]. Postoperatively, the patient receives a course of antibiotic treatment, usually for 6 weeks[82], followed by reimplantation of a new prosthesis when the clinician deems the infection resolved[12,83-85]. A combination of clinical judgment, aspiration, and serological data can aid the clinician's decision on appropriate time for reimplantation[12,82].

10. Patient Information about Their Prognosis

A patient diagnosed with a knee PJI should be informed about the prognosis. Providing information is key in maintaining realistic expectations, and avoiding medicolegal issues. Ideally, the patient's family should also be involved during the presentation of prognostic information.

Although the term "successful treatment" in PJI has been widely used, until recently, its definition was non-uniform. Our group found more than 10 different definitions of success in the current literature[86], thus, we decided to create a Delphi-based consensus definition. The study was published recently[86], and it described success as 1) infection eradication (characterized by a healed wound without fistula, drainage, or pain), and no infection recurrence caused by the same organism strain, 2) no subsequent surgical intervention for infection after reimplantation surgery; and, 3) no occurrence of PJI-related mortality (by causes such as sepsis, necrotizing fasciitis). We expect that in the near future this definition will help us better present prognostic information, and the overall probability to succeed to optimize patient understanding.

In terms of infection eradication, according to a meta-analysis by Jamsen et al.[87], the failure to eradicate infection after treatment of a periprosthetic knee infection ranged from 0%–31%. Recurrent infections occurred in 0%–18%, and new infections varied from 0%–31%[87]. Regarding functional outcomes, Barrack et al.[88], in a multicenter study of surgical outcomes following revision knee arthroplasty, patients demonstrated a lower Knee Society Score (KSS) in their cohort of septic revisions compared with revisions for aseptic failure. Concerning the radical management of failed TKA infection treatment, Chen et al.[89] demonstrated that patients with knee fusions had better functional scores than knee amputations.

In TKA revisions, Barrack et al.[88] demonstrated that revisions due to infection had no differences regarding patients' satisfaction compared with aseptic revision cases. This fact has been supported in a subsequent study by Patil et al.[90].

Conclusions

Knee PJI is a devastating complication that is faced by every knee arthroplasty surgeon. We suggest that PJI should be combated in an organized way, establishing institutional or even national protocols in order to decrease the variability in its prevention and management. Based on current knowledge, we highly recommend the inclusion of these ten strategies as preoperative, intraoperative, and postoperative measures to minimize the risk and consequences of periprosthetic knee infection.

Conflict of Interest

Javad Parvizi: Speakers bureau/paid presentations: Elsevier, Wolters Kluwer, Slack, Datarace; Consulting: Zimmer, Smith& Nephew, Convatech, TissueGene, Ceramtec, Emovi, 3M, Cadence, Medtronic, Pfizer; Stock: SmarTech, Hip Innovation Technology; Medical/Orthoapedics publications editorials/governing board: Journal of Athroplasty, Journal of Bone and Joint Surgery, Bone and Joint Journal; Service on Committees/Boards: Philadelphia Orthopaedics, Eastern Orthopaedics, CD Diagnostics, United Healthcare, Magnifi Group (Publishers), 3M.

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