Periprosthetic Joint Infections: A Review

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ABSTRACT

Joint replacement procedures are considered some of the most successful surgical procedures in orthopaedics. An increased demand for these procedures is expected owing to an aging population and improved techniques. Despite the success of these procedures, the complications can be devastating, especially periprosthetic joint infections. Considerable effort has been applied toward enhancing the understanding of the prevention, diagnoses, and treatment of these infections. In 2018, an international consensus meeting convened to discuss the most relevant issues in periprosthetic joint infections and to provide consensus based on published studies. Additionally, the criteria for periprosthetic joint infection diagnosis have been updated. The purpose of this review was to highlight a few topics of interest. The collective body of research in periprosthetic joint infections is massive and evolving, and surgeons should be aware of developments in this area that may improve patient care.

Keywords: Periprosthetic Joint Infection, Arthroplasty, Hip and Knee

INTRODUCTION

In the United States, more than 1 million joint replacements are performed annually, including an estimate of 7 million Americans living with a hip or knee replacement.[1] The incidence of infection after primary total knee and hip replacement is about 1% to 2%. The average annual cost for an infected total knee can exceed $100,000, nearly four times the cost of an uncomplicated procedure.[2] In 2009, the estimated cost to the United States healthcare system was $566 million, which is estimated to increase to $1.6 billion in several years.[3] Infection can lead to loss of function, increase in number of surgical procedures and hospital stays, and prolonged antibiotic administration with subsequent side effects. The morbidity and mortality of patients who experience a periprosthetic joint infection can be severe. Mortality rates can be grim, with an average of 22% at 5 years.[4]

Treating periprosthetic joint infections is challenging because they can vary considerably in presentation. The infections are usually considered to be either acute or chronic. Acute infections are established postoperatively by either direct inoculation or through hematogenous seeding. Various pathogens can cause periprosthetic joint infections. The most common is *Staphylococcus aureus* but the pathogen *Staphylococcus epidermidis* often presents in indolent chronic infections. There is no perfect test for confirming periprosthetic joint infections, and low virulent bacteria may evade our most sensitive detection methods. We are frequently unable to secure a culture, which creates challenges in deciding appropriate treatment. Complete eradication has proven extremely difficult, and much of that difficulty is attributed to the resilience of biofilms. Biofilms are a complex environment composed of bacteria within their extra cellular matrix. This adherent biofilm matrix provides protective properties to the bacteria residing in a sessile state, which makes both detection and treatment difficult. Biofilm creates an intricate system that can evade our immune system and enhance resistance to antibiotics by more than 1000 fold.[5]

The magnitude of problems regarding musculoskeletal infections has invoked international efforts. In 2018, a group of more than 600 international and multidisciplinary experts convened in Philadelphia to review questions regarding musculoskeletal infection. The Second International Consensus Meeting on Musculoskeletal Infection aimed to provide consensus on important topics in orthopaedic infections. Parvizi et al[6] recently redefined the diagnostic algorithm for periprosthetic joint infections. The attention on this topic is well deserved, but we have a long way to go. The purpose of this article is to examine a few topics regarding the prevention, diagnosis, and treatments of periprosthetic joint infections.

PREVENTION

Prevention is the first line of defense and most important step in addressing periprosthetic joint infections. Intense effort has been made to identify the host factors, especially modifiable factors that predispose patients to infections. Authors have proposed using scoring tools to help in the preoperative selection and optimization of patients.[7] Obesity is prevalent in prospective patients, and this host factor can notably increase complications. In regards to infection, there appears to be a linear risk with obesity. Surgeons may select different body mass index (BMI, kg/m^2) cutoffs; a common cutoff is 40 BMI. Patients with a BMI above this threshold have twice the risk

Major criteria (at least one of the following)	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

		Minor Criteria	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected
		Elevated ESR	1	
	Synovial	Elevated synovial *WBC count or LE*	3	**2-5 Possibly Infected [a]**
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 Not Infected
		Elevated synovial CRP	1	

	Inconclusive pre-op score *or* dry tap [a]	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected
	Positive histology	3	**4-5 Inconclusive [b]**
	Positive purulence	3	
	Single positive culture	2	≤3 Not Infected

Figure 1. *New scoring based definition for periprosthetic joint infection. Proceed with caution in: adverse local tissue reaction, crystal deposition disease, slow growing organisms. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LE, leukocyte esterase; PMN, polymorphonuclear; WBC, white blood cell. The superscript "a" indicates it is for patients with inconclusive minor criteria, operative criteria can also be used to fulfill definition for periprosthetic joint infections. The superscript "b" indicates to consider further molecular diagnostics such as next-generation sequencing. Figure reprinted with permission from Elsevier from The Journal of Arthroplasty, Vol 33, Parvizi J, Tan TL, Goswami K, et al, The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria, page 1312, 2018.*

of developing deep infections.[8] Bariatric surgical procedures can be highly effective in weight loss, but meta-analysis has not shown any considerable reduction in infections.[9] It is theorized that persistent malnutrition may be largely accountable.

In addition to identifying host factors, other preoperative measures have shown promising results in reducing periprosthetic joint infections. Screening for decolonization protocols and methicillin-resistant *Staphylococcus aureus* (MRSA) carriers still appear to be controversial with no conclusive evidence about utility and cost-effectiveness. Although concerns arise, cleansing the entire body preoperatively appears to be effective, particularly with chlorhexidine.[10,11] Using antibiotic cement in primary total joints continues to be controversial without conclusive evidence. In consideration of antibiotic stewardship, its use should likely be reserved for specific indications. One indication of the controversy is the split vote among delegates during the Second International Consensus Meeting on Musculoskeletal Infection. Preoperative systemic antibiotics is a mainstay and a recommendation by the American Academy of Orthopaedic Surgeons; however, novel antibiotic delivery techniques may prove to be more effective when delivering concentrations of antibiotics to the tissues at the surgical site. Chin et al[12] showed that administration of intraosseous vancomycin after tourniquet inflation resulted in nearly ten times the tissue concentrations around the knee compared to systemic antibiotics. There is still no evidence to support topical vancomycin at wound closure in total joints. The evidence for its use is isolated to retrospective spine studies.

Operating time efficiency has been shown to decrease infection rates in several surgical fields, but suction tips may be an overlooked source of intraoperative contamination.[13] Givissis et al[13] found that 66% of suction tips had positive cultures after 1 h of operating room time, with the predominant bacteria being *Staphylococcus aureus*. It may be reasonable to change suction tips during prolonged surgical procedures and avoid leaving suction tips in surgical wounds owing to risk of air contaminants. A common risk factor for infections are allogeneic blood transfusions. Blood transfusions have an immunoprophylaxis effect, and a two-fold risk of infection has been observed after one unit of transfused red blood cells.[14] Although no current research shows a

direct effect of tranexamic acid on infection reduction, its use has recently become widespread as a safe and cost-effective blood saving modality. In one randomized controlled trial (RCT) of total knee arthroplasties, use of intraarticular tranexamic acid resulted in a decreased blood transfusion rate of 16.7% to 1.3%.[15]

Studies have suggested that dilute betadine solution reduces infection during surgical wound closure. Brown et al[16] reported a reduction in primary joint infections using a dilute 0.35% betadine wash for 3 min. Compared to saline, the rate of infection decreased from 0.97% to 0.15%. There are novel closure techniques in total joint arthroplasty (TJA) but still no concrete evidence to support one modality over others. A recent and large RCT that investigated antimicrobial sutures in total joint replacement showed no difference in surgical site infection rates.[17] There is some support for occlusive silver impregnated dressings in several studies, including one prospective RCT that described silver dressings as an independent factor reducing periprosthetic joint infections.[18]

Finally, genetics is an uncommon host factor that may explain infections in apparently healthy individuals. It is suggested that some patients may have subclinical immune deficiencies. A massive population-based study (66,000 patients with TJA) has identified familial clustering of periprosthetic joint infections.[19] Investigators identified pedigrees with excessive clustering of periprosthetic joint infections that did not seem attributable to other risk factors. Other investigations have also implied genetic susceptibility. For example, a study out of the Czech Republic found that variations of the innate immunity protein, mannose-binding lectin, is linked to susceptibility to periprosthetic joint infections.[20]

DIAGNOSIS

Unfortunately, there is no perfect test for diagnosing periprosthetic joint infections and this presents a challenge. For example, culture test results can return negative, findings of serological tests are not sensitive, and modern synovial assays have limitations and results can yield false-positives and false-negatives. In 2011, the Musculoskeletal Infection Society proposed criteria to define periprosthetic joint infections.[21] The original Musculoskeletal Infection Society criteria were an important step in standardizing the definition and eliminating subjectivity in diagnosing periprosthetic joint infections. In the 2013 Initial International Consensus Meeting, these criteria were revised and recently updated again by Parvizi et al[6] in 2018. The new definition includes some novel markers such as synovial alpha defensin and synovial C-reactive protein (CRP). The scoring system is now weighted, and its design makes it easier to achieve preoperative diagnosis. When validated against an external cohort of patients, the new criteria exhibited improved results compared to original Musculoskeletal Infection Society criteria with a sensitivity of 97.7% and specificity of 99.5%.

Another indicator of periprosthetic joint infections is alpha defensin, an antimicrobial peptide generated by neutrophils. Alpha defensin may be the most accurate test for detecting periprosthetic joint infections; however, caution must be used in certain settings. Alpha defensin is not indicated in the early postoperative period and may yield false-positive results for metallosis. When diagnosing periprosthetic joint infections, Stone et al[22] proposed an algorithm that used synovial CRP in combination with alpha defensin to reduce false-positive and false-negative rates.

Obtaining cultures is ideal in treating periprosthetic joint infections because it allows guidance on treatment protocols and the ability to target antibiotics. Despite best practices, negative culture results are common. Notably, obtaining multiple tissue samples can improve sensitivity of growing a pathogen. Synovial fluid should also be obtained when possible and blood culture vials may further enhance sensitivity.[23] It has been shown that culture swabs have high false-positive rates. If implants are removed, sonication can improve sensitivity of cultures from 60% to 80%.[24] It is suggested to incubate cultures for longer times if low virulent pathogens are suspected; additionally, repeating aspiration and culture tests is suggested if initial culture findings are negative.[25]

Despite our best culturing techniques, many culture findings are negative for infection, which presents a treatment dilemma. A novel application of genetic sequencing may find a larger role in diagnosing periprosthetic joint infections.[26] Compared to traditional sequencing techniques, next-generation sequencing is a technology with reduced time and costs. Next-generation sequencing expands on prior polymerase chain reaction sequencing techniques. This allows DNA to be extracted from samples and sequenced in automated fashion to identify present pathogens. Furthermore, next-generation sequencing provides the ability to identify antibiotic resistance genes and has the potential to obtain results faster than cultures and detect pathogens in recent antibiotic administration. However, this technology is still in its infancy, and these techniques have shown to be extremely sensitive at detecting bacterial DNA—even to the point of detecting bacterial DNA in synovial fluid of native joints.[27] These investigations may bring to light the concept of host colonization versus true infection.

TREATMENT

The initial treatment decision for periprosthetic joint infections is usually between implant retention or implant exchange, either one-stage or two-stage. Debridement, antibiotics, and implant retention (DAIR) can be successful in some situations. Important prognostic factors for successful DAIR include host factors, timing of operative treatment, pathogen involved, exchanging modular components, aggressive debridement, and appropriate use of antibiotics.

Several factors make DAIR appealing, including reduced surgical morbidity to the patient and reduced cost of treatment if successful. Reported success rates for DAIR vary but are generally less successful than a full-component explant technique.[25]

To enhance biofilm eradication, different antiseptics as adjuncts to mechanical debridement have been investigated. Antiseptics have advantages of reaching areas of the joint that are difficult to mechanically debride. In the era of antibiotic resistance, they may prove to be a useful addition. Chlorhexidine, betadine, hydrogen peroxide, detergents, acetic acid, and even honey have been discussed in combatting biofilms; additionally, some of these have been used in vitro experiments and have shown chlorhexidine to be effective in biofilm eradication.[28,29] Proprietary solutions have recently become available and are purported to be effective in disrupting the extracellular matrix of biofilms. In vitro studies have recorded the ability of proprietary solutions to reduce biofilms; however, clinical trials are still pending.[30]

Two-stage exchange of periprosthetic joint infections has reported some of the highest success rates and remains the gold standard in the United States. On the other hand, one-stage exchange is an attractive option and has been shown to be effective in certain situations. The appeal of a one-stage exchange is quicker recovery, better functional outcomes, less surgical-related morbidity, and decreased hospital stays and costs. However, patient selection is critical and the ideal candidates are healthy with an identified non-resistant organism. Currently, no RCT directly compares one-stage to two-stage exchange. However, when the techniques were used on total knees, a meta-analysis found similar recurrence rates of infection at 2 years.[31] Unfortunately, failure rates remain high regardless of treatment. Ford et al[32] recently reported a reinfection rate of 27% in two-stage exchange patients who underwent re-implantation. Sadly, many patients never obtain a successful re-implantation and end up deceased, living with a spacer, or undergoing salvage procedures such as arthrodesis or amputation.

Other approaches to treating periprosthetic joint infections have been described. Whiteside et al[33] used intraarticular antibiotic infusions in a cohort of 18 patients with MRSA prosthetic joint infections. For 6 weeks postoperatively, all 18 patients received intraarticular catheter infusions of vancomycin without the addition of systemic antibiotics. Seventeen patients were infection-free at the minimum follow-up of 27 months.

Immunoprophylaxis are vaccines that may enhance the ability of our immune system to combat bacteria. These are currently being investigated in treating periprosthetic joint infections.[34] Bacteria that are multidrug resistant are effectively threatening the era of antibiotics. Pneumococcal vaccines have been shown to prevent meningitis from cochlear implant-associated infections.[35] *Staphylococcus aureus* vaccines have been studied, with guarded results, in patients with cardiothoracic and hemodialysis.[36,37] A novel *Staphylococcus aureus* vaccine is currently under study. The purported advantage of this vaccine is that it targets virulent factors involved in the establishment of infection. This multi-antigen staph vaccine has been shown to induce an immune response in a stage 1 clinical trial.[34] There is now a stage 2 clinical trial underway that is investigating the vaccines' ability to prevent infection in patients undergoing spine procedures. Additionally, studies are currently examining another pathway that disrupts biofilms: the utilization of biologic compounds to disrupt bacterial communication.[38] These are known as quorum-sensing inhibitors, and these agents may be a last line of defense in the face of antibiotic resistance.

CONCLUSION

Periprosthetic joint infections present a complex challenge to our society. We are bound to see more infections with the increasing number of joint replacement procedures, which leads to staggering patient morbidity, patient mortality, and costs to our healthcare system. We continue to evolve our understanding of these infections; however, bacteria are evolving as well and antibiotic resistance is concerning. New approaches in prevention, diagnosis, and treatment of these infections will hopefully improve our ability to minimize these devastating complications.

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