Review Article

Periprosthetic joint infection: Current concept

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Abstract

Periprosthetic joint infection (PJI) is one of the most devastating and costly complications following total joint arthroplasty (TJA). Diagnosis and management of PJI is challenging for surgeons. There is no "gold standard" for diagnosis of PJI, making distinction between septic and aseptic failures difficult. Additionally, some of the greatest difficulties and controversies involve choosing the optimal method to treat the infected joint. Currently, there is significant debate as to the ideal treatment strategy for PJI, and this has led to considerable international variation in both surgical and nonsurgical management of PJI. In this review, we will discuss diagnosis and management of PJI following TJA and highlight some recent advances in this field.

Key words: Periprosthetic joint infection, total joint arthroplasty, diagnosis and treatment of periprosthetic joint infection

Introduction

Given the increase of total joint arthroplasty (TJA) being performed annually, the number of complications necessitating revision surgery is increasing.[1,2] Periprosthetic joint infection (PJI), one of the major complications and etiologies of implant failure after TJA, is associated with substantial financial burden on the healthcare system and significant physical and psychological morbidity on patients.[3]

Using the nation-wide in-patient sample (NIS) data, Kurtz *et al*. found the relative incidence ranged between 2.0% and 2.4% of total hip arthroplasties (THA) and total knee arthroplasties (TKA).[3] However, single institution studies using more precise definitions for PJI, reported lower rates ranging from about 0.6% to 0.9%.[4,5] In spite of the relatively low incidence of PJI, the financial burden remains enormous. The annual cost of infected revisions to U.S. hospitals increased from $320 million in 2001 to $566 million in 2009, and it is estimated that the cost will exceed $1.62 billion by 2020.[3]

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Access this article online	
Quick Response Code:	Website: www.ijoonline.com
	DOI: 10.4103/0019-5413.106884

Pathophysiology of periprosthetic joint infection

Adherence of bacteria to the implant is the first step in pathogenesis of PJI.[6] Two distinguishable phases of reversible (non-specific) and irreversible (specific) attachments occur during bacterial adhesion to the surface of the implant.[6] The reversible attachment works based on nonspecific physical and chemical characteristics of the bacteria. Biomaterial and surrounding joint fluid also play a role in reversible adhesion of the bacteria to the implant. In contrast, irreversible adhesion depends on more specific structures and receptors.[6]

Biofilms play an important role in pathogenesis of PJI.[7] Biofilm is a complex structure comprised of microorganisms enveloped in macromolecules of glycocalyx and other protective structures.[8,9] Attachment of bacteria to a surface involves cell-to-cell adhesion between microorganisms and the artificial surface.[10]

Evidence suggested intracellular internalization of staphylococci as a mechanism contributing to pathogenesis of PJI and resistance to treatment.[10,11] According to this concept, staphylococci can invade and live inside the host cells, facilitating long term persistence of the microorganism in bone via evasion of antibiotics and immune system responses. "Small colony variant" strains are particularly skilled in invading and living inside the host cells. These strains have mutations that impair the electron transport pathway.[12]

A majority of PJI's are caused by Gram-positive cocci (*Staphylococcus aureus* and coagulase-negative Staphylococcus).[4,13] On occasions, Gram-negative bacteria[14,15] and fungi[16] may also result in PJI. A considerable proportion of PJIs can be polymicrobial. In a study

by Marculescu and Cantey, 19% of PJI episodes were polymicrobial.[17]

Definition and manifestations of periprosthetic joint infection

According to the proposed criteria by the Musculoskeletal Infection Society (MSIS), PJI exists when

1. There is a sinus tract communicating with the prosthesis or
2. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or
3. Four of the following six criteria exist.
    - Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration, elevated synovial white blood cell (WBC) count, elevated synovial neutrophil percentage (PMN%), presence of purulence in the affected joint, isolation of a microorganism in one culture of periprosthetic tissue or fluid, or greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification.

PJI may also be present if fewer than four of these criteria are met and clinical suspicion is high.[18]

Early PJI (occurring <3 months after index surgery) usually manifests with acute joint pain, wound inflammation (warmth and erythema), joint effusion, and loss of function.[7,19] Sinus tract and purulent drainage may also develop in some cases.[7] Chronic PJI usually presents with chronic joint pain and loosening of the prosthesis.[7,19]

Diagnostic work up

Based on guidelines by the American Academy of Orthopaedic Surgeons (AAOS), workup for diagnosis of PJI starts with ordering ESR and CRP due to their high sensitivity and acceptable specificity. In the presence of normal level of these tests, infection is "unlikely," however, abnormal levels of either test should prompt further investigation in the form of joint aspiration. The combination of serology and the aspiration can help the clinician confirm or refute diagnosis of PJI.[20] The combination of serology and joint aspiration is adequate for diagnosis of PJI in the majority of cases. In a very select few, in whom PJI is suspected but cannot be confirmed, additional tests such as nuclear imaging may be ordered.[20]

Culture of aspirated joint fluid and samples taken intraoperatively has an important role in diagnosis of PJI. It is recommended that three to five samples from various locations around the prosthesis be taken to increase the likelihood of obtaining positive culture. Culture-negative PJI has been reported in 7% of PJI episodes.[21]

Prior antibiotic use, slow growing organisms, and presence of biofilms are some of the factors negatively influence sensitivity of culture results.[22] In a systematic review of literature, Larsen *et al*. suggested some strategies to improve culture methods for diagnosis of PJI.[22] They suggested cultures obtained from the diluents after sonication of implants is a better method compared to cultures obtain from tissue biopsies. Their findings demonstrated that culture of synovial fluid in blood culture vials is more sensitive compared to intraoperative swab cultures and tissue cultures.

ESR and CRP are standard screening tests for any patients undergoing revision TJA regardless of the cause of failure.[20] Based on previous definitions for PJI, Ghanem *et al*. defined cutoff values for ESR and CRP for diagnosis of PJI.[20] They showed that ESR of 30 mm/hr and CRP of 10 mg/L have sensitivity of 94.3% and 91.1%, respectively. Combining both ESR and CRP increased the sensitivity to 97.6%. However, based on the new definition of PJI that has been proposed by the MSIS, the threshold of ESR and CRP for diagnosis of PJI would be higher. Using the MSIS definition for PJI, optimal cut-off points for ESR were 48.5 mm/hr and 36.5 mm/hr in hips and knees, respectively [Unpublished data]. For CRP, 13.5 mg/L and 23.5 mg/L were cut-off values in hips and knees, respectively. Combining ESR and CRP yielded sensitivity of 87.6% for hips and 88.1% for knees. The specificity was 92.1% for hips and 96.4% for knees.

In a meta-analysis of 3909 revision TJA, Berbari *et al*. assessed accuracy of available inflammatory markers for diagnosis of PJI.[23] They found the diagnostic odds ratio of 314.7 for interleukin-6, 13.1 for serum CRP level, 7.2 for ESR, and 4.4 for white blood-cell count. However, only three studies had evaluated the role of interleukin-6, which is not used routinely in clinical practice. Data from our institution also showed low sensitivity and specificity of serum white blood cell count and its differential for diagnosis of PJI.[24] Therefore, these tests do not have value in diagnosis of PJI and should not be routinely ordered as a part of PJI work up.

There is strong evidence supporting performing hip and/or knee aspiration as part of PJI work up in patients with abnormal levels of either ESR or CRP.[20] Repeating the joint fluid aspiration is a reasonable approach in patients with abnormal ESR and/or CRP in whom synovial fluid analysis is negative in the first attempt of synovial fluid aspiration. Available evidence indicates that either a synovial fluid WBC count >1700 cells/μL (range: 1100 to 3000 cells/μL) or a neutrophil percentage >65% (range: 64% to 80%) is highly suggestive of chronic PJI.[20] A frozen section can also be used for diagnosis of PJI. A frozen section is a

very good "rule-in" test but has relatively low value as a "rule-out" test.[20] Compared to 10 neutrophils in high power microscopic field, lower number of neutrophils may have similar sensitivity but lower specificity.[20]

Advances in diagnosis of periprosthetic joint infection

Given the limitations of available diagnostic tests for PJI, in recent years an attempt has been made to identify new tests that can help surgeons more accurately detect patients with real PJI. Leukocyte esterase strips, measure of inflammatory biomarkers in the synovial fluid, and Ibis T5000 universal biosensor are some of these advances that will be described briefly.

Leukocyte esterase

Leukocyte esterase is an enzyme secreted by activated neutrophils that have migrated to the site of infection. A colorimetric strip test for this enzyme has been in use for decades for diagnosis of urinary tract infection. The color of the reaction on the strip is either negative (no color change), trace, + or ++. The use of leukocyte strip for diagnosis of PJI was recently described by Parvizi *et al.*[25] They found sensitivity of 80.6% and specificity of 100% if ++ was used as an indication of PJI. Positive and negative predictive values of the test were 100% and 93.3% respectively. A recent study by other authors also confirmed high sensitivity and specificity of leukocyte esterase.[26] Using a synovial fluid white blood cell count of greater than 3000 cells per microliter as an indicator of PJI, the sensitivity and specificity of the leukocyte esterase strips were 92.9% and 88.8%, respectively. When using positive cultures for diagnosis of PJI, sensitivity and specificity of leukocyte esterase strips were found to be 93.3% and 77.0%, respectively.[26]

The advantage of the inexpensive leukocyte esterase test is that it relies on one drop of synovial fluid for determination of PJI and can be performed in one minute. The main disadvantage of the test is that it cannot be performed with blood stained fluid due to its reliance on a colorimetric change. At our institution we utilize micro-centrifuge and/or filters to remise blood contamination of the synovial fluid. The leukocyte esterase test has become part of diagnostic work up of patients with suspected PJI at our institution.

Synovial fluid inflammatory markers

Measurement of inflammatory markers in synovial fluid has shown promising initial results. In a series of 14 patients with PJI and 37 cases without infection, synovial fluid interleukin-1 and interleukin-6 could detect all infected cases.[27] In another study, synovial fluid CRP level showed a sensitivity of 85% at a threshold of 9.5 mg/L while specificity and accuracy of the test were 95% and 92%, respectively.[28] In spite of promising preliminary results, further studies are required to confirm diagnostic value of synovial fluid CRP and other synovial inflammatory markers for diagnosis of PJI.

Ibis T5000 universal biosensor

The Ibis T5000 universal biosensor which operates based on broad-range polymerase chain reaction (PCR) and high-performance mass spectrometry seems to be more accurate than conventional PCR.[29] We recently used this technique in patients who underwent total knee revision with preoperative diagnosis of aseptic failure.[30] Although this technique could identify few cases with occult PJI, like the conventional PCR technique, Ibis biosensor also showed high false positive rate.

Management of and outcomes after treatment for periprosthetic joint infection

Although making an accurate and efficient diagnosis of PJI is often a challenge in itself, some of the greatest difficulties and controversies involve choosing the optimal method to treat the infected joint. Currently there is significant debate as to the ideal treatment strategy for PJI, and this has led to considerable international variation in both surgical and nonsurgical management of the devastating complication. In this section we will review the different options available for the orthopaedic surgeon to manage PJI and outcomes associated with each approach.

Irrigation and debridement

Traditionally, irrigation and debridement (I and D) with exchange of the modular prosthetic components has been treatment of choice in acute postoperative and acute hematogeneous PJI.[31] This was largely in part due to the idea that with acute infection, bacteria had not yet formed an impenetrable glycocalyx biofilm layer along the prosthetic components.[32] Theoretically then, by undertaking an I and D, one could diminish the bacterial load in the joint and retain fixed implants, thereby minimizing patient morbidity. More recently, it has been suggested that depending on timing of infection symptoms, pathogenicity of infecting organism, and immune status of infected patient, an I and D may not in fact be initial procedure of choice for all acute PJI.

The role of symptom onset relative to the index joint procedure has been studied with regards to the success of I and D in treating PJI. Reports by Marculescu *et al.* and other authors have concluded that the duration of symptoms directly impacts the infection eradication rate after I and D.[31,33,34] On the other hand, Koyonos *et al.* showed that when comparing outcomes after I and D, acute postoperative (<4 weeks), acute delayed (acute onset symptoms >4 weeks from index surgery), and chronic PJI all showed relatively equal rates of infection eradication.[35]

With regards to infecting organism, there is much controversy surrounding the role of organism virulence and antimicrobial resistance profiles on failure of I and D procedures. Some authors have published that infections with Staphylococcal species lead to relatively low success rates of 65-70% after I and D.[35,36] Furthermore, infections with methicillin resistant Staphylococci have been shown to lead to even lower success rates of 16-28% after I and D.[37,38] Another recent study by Odum *et al*., however, refutes the conclusion that infecting organism plays a significant role in predicting failure after I and D, showing relatively poor, yet equal failure rates for I and D of PJI with organisms of all resistance.[39]

Finally, the health status of the patient with PJI has been shown to affect the outcome after I and D. Segawa *et al*. and Silva *et al*. both showed that patients with compromised wound healing secondary to medical conditions including rheumatoid arthritis, diabetes mellitus, and chronic renal failure, did worse after I and D for PJI.[40,41] On the contrary, a small study by Odum *et al*. did not find significance when comparing outcomes after I and D between patients with different American Society of Anesthesia (ASA) scores (proxy for medical comorbidity severity).[39]

Although previously believed to play a definitive role in treatment of acute PJI, recent evidence has brought into question what role if any I and D has in management of total joint infections. Sherell *et al*. even concluded that patients who initially failed I and D treatment, went on to have less than 70% infection eradication rate after a two-stage exchange arthroplasty was undertaken.[42] Due to its easy and efficient procedural technique, I and D will always remain an appealing option for treating PJI. However, orthopedic surgeons must be aware that by choosing this method in all acute PJI, they may in fact be increasing rather than minimizing patient morbidity and ultimately jeopardizing patient outcomes.

One-stage exchange arthroplasty

While two-stage exchange arthroplasty is treatment of choice for PJI in the United States, many European centers have long advocated the use of a single stage procedure, citing decreased morbidity, lower cost, and comparable outcomes. In part due to the increasing importance of hospital burden, the one stage approach is garnering a renewed interest all over the world. The main agreement between all published works on the topic of one-stage exchange is that in order to ensure adequate results, appropriate patients must be selected and meticulous surgical technique must be followed.

Regarding appropriate patient selection, authors have reported that host factors, organism factors, and local factors all play important roles in determining success after one stage exchange. Oussedik *et al*. delineate that in order for a patient to be a candidate for single stage treatment, they must have healthy soft tissues, minimal bone loss, and known infecting organism with antibiotic susceptibility.[43] In the United States, a greater rate of methicillin-resistant organisms may in part contribute to the overall hesitancy to treat PJI with this method.

There is scare literature from the United States on one-stage exchange arthroplasty. In existing publications, there remains substantial variability in surgical technique, patient inclusion criteria, and postoperative medical management of patients.[44] In Europe much of the success of the one-stage procedure is attributed to a radical synovectomy and debridement of soft tissues in conjunction with addition of postoperative systemic antibiotic administration.[45] Success rates after one-stage exchange arthroplasty in European centers have been cited to be as high as 81.9% at 40.7 months mean followup by Romano *et al.*, and even 100% at minimum 2 year followup by Klouche *et al.*[46,47]

Overall outcomes in single stage exchange arthroplasty have been improving over the years. Reporting on PJI of the hip, a systematic review of more than 1200 patients in 12 studies by Jackson *et al*. showed overall 83% infection eradication rate after one stage exchange.[44] They reported negative predictors to be frequently associated with type of infecting organism with polymicrobial, gram negative, and methicillin-resistant organisms yielding the worst outcomes. In a review of eight studies with 37 patients undergoing single stage exchange for PJI of the knee, Silva *et al*. found an 89% infection eradication rate.[41]

The use of strict exclusion criteria in selecting patients eligible for one-stage exchange cannot be overemphasized. However, with the continued emergence of antibiotic resistant organisms responsible for PJI, and the deteriorating health of elderly joint arthroplasty patients, these criteria will inevitably lead to fewer one-stage procedures being performed. Nonetheless in a healthcare environment where costs and reimbursement are increasingly scrutinized, the option for a cost-saving single procedure to treat PJI will continue to garner renewed interest around the world.

Two-stage exchange arthroplasty

Treatment of PJI with two-stage exchange arthroplasty has been utilized for more than four decades.[48] The first stage involves complete resection of all foreign material, debridement of surrounding infected soft tissues, and placement of an antibiotic impregnated cement spacer. The second stage involves removal of the spacer and any additional necrotic tissues, thorough irrigation, and placement of new prosthetic implants.

In the United States, chronic PJI has been mainly treated via two-stage exchange arthroplasty with a 4 to 8 week course of IV antibiotics in between the two stages.[49-52] However, this surgical strategy is now described as initial treatment for some acute postoperative or acute hematogeneous PJI. Specifically, acute infection in immune compromised hosts with high virulence-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) may best be treated with initial two-stage exchange.[42] Furthermore, in cases of acute PJI where an initial attempt at more conservative surgical treatment such as I and D or one-stage exchange have failed, use of subsequent two-stage exchange procedures have been indicated.[53]

The two-stage method is beneficial for several reasons. Spacers not only allow for increased joint stability, but also prevent soft tissue contraction and facilitate reimplantation procedures.[48,54,55] In addition, local antibiotic cement allows for high bactericidal activity directly at the site of PJI, adding to the intraarticular concentration of antibiotics while minimizing systemic toxic effects of parenteral therapy.[50,55-60] Perhaps most importantly, however, is the time patients have without foreign prosthetic material inhabiting their joint during infection eradication.

An important consideration when using cement spacers is the incorporation of specific antibiotics into the cement. Due to their broad antibacterial coverage and favorable mixing properties, the most commonly used combination of antibiotics in spacers is powdered tobramycin and vancomycin in polymethylmethacrylate cement.[50,61,62] A wide variety of antibiotic concentration ratios are used internationally but in general no more than 8 g per 40 g of cement should be utilized to minimize systemic side effects.[63] While the majority of the antibiotic elution takes place during the first days after placement, some studies have shown local cement spacers achieve supratherapeutic levels of antibiotics even after several weeks.[50,55-60]

One of the most controversial aspects of the two-stage exchange procedure today is the decision between using static versus articulating spacers. While certain situations such as extensive bone loss prohibit the use of articulating spacers, debate remains as to the optimal choice.[64,65] Hand molded static spacers have been shown to limit knee range of motion and functionality between the two stages, and can lead to ultimate worse functional outcomes after reimplantation.[66-68] Meanwhile articulating spacers, which are contoured to the native joint to resemble a prosthetic implant, have come into recent favor with commercial products allowing for ready to use spacers or highly efficient molding kits. The first of these articulating spacers to become popular was the "prosthesis with antibiotic-loaded acrylic cement" (PROSTALAC) spacer for the hip. There are several potential advantages to articulating spacers including increased joint mobilization and patient satisfaction between stages.[69,70] However, the significant disparity in cost compared to their cheaper static counterpart (approximately $500 vs. $3500) has prevented articulating spacers from coming into universal favor from joint surgeons.[71] While articulating spacers for the knee have gained significant favorability due to previously mentioned advantages over static spacers, there is a relative paucity of literature delineating distinct advantages of articulating spacers for the hip suggesting further evidence is needed before adopting them for routine use to treat hip PJI.

In certain immunocompromised patients who cannot tolerate a reimplantation procedure, definitive treatment ends after resection of infected prosthesis or even with amputation of involved limb.[53] For all others, the decision must be made when to reimplant new prosthetic implants. Unfortunately, no dependable method to date has been established to ensure adequate clearance of infection prior to reimplantation surgery. A study by Kusuma *et al.* showed that even inflammatory markers ESR and CRP as well as synovial WBC count and differential were unreliable in detecting persistent versus treated infection.[72] Therefore, currently accepted practice is to administer 4 to 8 weeks of IV antibiotics followed by a joint aspiration with the patient off of antibiotics for minimum of two weeks. Fluid obtained from the aspiration is then cultured to evaluate for any organism growth, and if the patient's inflammatory state has been trending downward, they are deemed candidates for reimplantation surgery. During reimplantation surgery, it is crucial to both evaluate the deep joint space for visual evidence of uncleared infection and to take several tissue and fluid samples for additional postoperative cultures. Another question that has not been adequately answered in the literature is how to use the results of the cultures taken during reimplantation if they come back positive for organism growth. Thus, it can be seen that while two-stage exchange procedures are most commonly used for management of PJI, much remains uncertain during the second stage of treatment.

A major reason some consider two-stage exchange arthroplasty to be the "gold standard" treatment of PJI is the superior success rates and patient outcomes of this approach when compared to other treatment strategies. Overall, infection eradication using two-stage exchange is quite high, ranging from 85% to 100% for both the hip and knee joint, and does not depend on the type of antibiotic loaded cement spacer used.[66,73-75] Patient satisfaction and joint functionality are improved as well particularly in knee arthroplasty, with Meek *et al.* showing good WOMAC pain and functional scores after revision. Although the benefits

of the articulating spacer over the static variety have been proven in the knee joint, further randomized control trials with standard methods for spacer formation must be undertaken to warrant significant expenditure on their routine use in treating PJI.

Chronic oral antibiotic suppression therapy

While antibiotic suppression therapy may be utilized after reimplantation following a two-stage exchange, chronic antibiotic suppression alone may be reserved in those patients with immune compromise or comorbidities too significant to undergo a surgical procedure. These patients are likely at a higher risk of morbidity and mortality if undergoing surgery than they would be from their PJI alone.

There is not a substantial amount of literature regarding treatment of PJI with chronic antibiotic suppression alone with no surgical interventions. A case series by Segreti *et al.* evaluated 18 patients who underwent surgical debridement, retention of prosthesis, administration of intravenous antibiotics for 6-8 weeks followed by prolonged oral antibiotic suppression.[76] They found 15 of the 18 patients were able to retain functional prosthesis, and just 4 patients experienced antibiotic-related complications that did not require discontinuation of therapy.

Another study by Rao *et al.* similarly examined outcomes of 36 patients undergoing irrigation and debridement, retention of prosthesis, systemic intravenous antibiotic administration, followed by oral antibiotic suppression.[77] They found a use of suppressive antibiotics for a mean of 52.6 months led to favorable results in 86% of patients with retention of prosthesis at mean followup of 5 years.

Strong evidence from standardized clinical trials is lacking for surgeons to appropriately select specific patients who would do better with chronic antibiotic suppression rather than exchange of components. However, in those patients who are simply too high risk to undergo any surgical intervention requiring removal of prosthesis, antibiotic suppression may be a viable option that should not go without consideration.

Conclusion

Although proposing the new criteria by the MSIS committee for definition of PJI solved the lack of standard definition for PJI, there is still no single "gold standard" test for diagnosis of PJI. Therefore, a combination of tests for work up of patients with suspected PJI is recommended. Currently, ESR and CRP are the best available screening tests for PJI. Abnormal ESR and CRP necessitate further evaluation for probable PJI. Even after accurate diagnosis of PJI, there remain countless unanswered questions surrounding the optimal treatment modality. Currently, two-stage exchange arthroplasty serves as the gold-standard method for clearance of chronic infection, whereas the more conservative procedure of one-stage exchange is garnering renewed interest in certain subsets of patients. Regardless of the method used for treatment, the future in PJI research will tell surgeons whether to focus on true eradication of pathogenic organisms from an infected joint or on optimizing patient function and satisfaction after this devastating complication.

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How to cite this article: Aggarwal VK, Rasouli MR, Parvizi J. Periprosthetic joint infection: Current concept. Indian J Orthop 2013;47:10-7.

Source of Support: Nil, **Conflict of Interest:** None.