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Two-stage Revision in Periprosthetic Knee Joint Infections

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Abstract

Periprosthetic joint infections (PJIs) after total knee arthroplasties are among the most catastrophic and costly complications that put a huge burden on patients' wellness as well as the economy. The road to diagnosing and treating PJIs is challenging as there is still no gold standard method to reach the diagnosis as early as desired. There are also international controversies regarding the decision on the best approach to manage those cases. In this review, we highlight the recent advances in managing PJIs following knee arthroplasty surgery and discuss in depth the two-stage revision method.

INTRODUCTION

Due to the recent advancements in medicine, the life expectancy of the general population has increased. Given the modern lifestyle, people are having higher expectations for physical activity and mobility and hence the requirement for joint replacement surgery has surged. [1,2] Around a million knee and hip arthroplasty procedures are currently performed annually in the United States and this number is anticipated to double by 2030. [3] Alongside this increment in the amount of joint arthroplasty surgeries, the incidence of PJI also continues to rise. [2] Currently PJIs occur in 1% to 2% of primary and 4% of revision arthroplasties. [1,2,4,5] Kurtz *et al* [1] suggested that there will be over 260,000 revision total knee arthroplasties (TKAs) performed in the USA by 2030. Compared to hip arthroplasty, the risk of PJI is higher after knee arthroplasty. [6,7] In most centers, the rates of PJIs reported after TKAs vary from 0.5 to 2

percent and 0.5 to 1.0 percent is reported after total hip arthroplasties (THAs). A higher risk of PJI following TKAs may be attributed to the less protective soft tissue coverage and higher joint mobility. [8,9] Delanois *et al* [10] reported that PJI alone accounted for (20.4%) of all revisions after TKAs and this was considered the most common etiology leading to revision surgery. A number of risk factors are associated with developing PJIs including the operative setting, patient comorbidities and implant-related factors. [2] Additionally, the longer the implanted prosthesis is expected to last, the greater the cumulative risk is for developing infections during the entire implant life. Diagnosing PJIs early can reduce the significant physical and emotional burden on the patient and the financial pressures on the society. However, it is still challenging to do so due to the lack of diagnostic tests that are highly sensitive and specific. Therefore, the combination of early clinical suspicion alongside serological markers, radiological examinations, joint aspirates, and biopsies continues to be our main workforce for diagnosing PJIs. [11,12] The management of PJIs remains controversial and requires complex therapeutic approaches, prolonged antimicrobial therapy, and a variety of surgical techniques. Selecting the optimal treatment strategy to eradicate the infection requires proper diagnosis of the infecting microorganism(s) and identifying their antibiotic susceptibility. When PJIs are missed or inadequately treated, the patient will endure several operations due to the persistence of infection and this negatively impacts their function and quality of life. [13] Interdisciplinary approach is crucial to reaching the best-desired outcomes and this requires the involvement of orthopedic and plastic surgeons, infectious disease physicians as well as microbiologists. [2,14] The greatest difficulty in managing PJIs is the formation of the so-called biofilm, which enables the pathogens to remain on the implant surface and makes them resistant to most systemic intravenous antibiotics. Understanding this phenomenon helps in diagnosing and treating PJIs. [2] For example, using modern diagnostic methods such as sonication for biofilm detection, increases the sensitivity for diagnosing PJI, especially in chronic infections caused by low-virulence pathogens. [2]

In this review, we provide an updated summary of the current concepts surrounding the two-stage revision procedure in periprosthetic knee joint infections.

Definition & Classification of PJI

As there currently exists no single test that is capable of diagnosing PJIs with complete accuracy, this condition continues to be extremely challenging to tackle. [15–17] The Musculoskeletal Infection Society (MSIS) and the Infectious Diseases Society (IDSA) proposed criteria to help physicians diagnose PJIs. [18,19] In 2018, a second consensus meeting validated the MSIS definition of PJI but made a few minor modifications. [20] Whilst the major criteria for PJI are the same across all PJI definitions, the minor criteria or the supporting evidence vary and are less universally agreed upon. Lately, new tests and biomarkers have evolved and become freely available [21–23] including serum D-dimer [24] synovial leukocyte esterase (LE) [25] synovial alpha-defensin [26] synovial C-reactive protein (CRP) [27] and molecular techniques such as next-generation sequencing. [28] However, recent research has demonstrated the variability in those tests' accuracy (sensitivity and specificity). [29] Therefore, such advancements in PJI diagnosis demanded revising the existing diagnostic criteria to ones that incorporate the new testing and take into account the relative weights of the different tests included. Thus, a multi-institutional study was published in 2018 in the Journal of Arthroplasty and included new diagnostic criteria. [17] The new PJI scoring system outperformed the IDSA and MSIS criteria in terms of sensitivity and specificity. The proposed new criteria are summarized in Table 1. The timing in which infection occurs can aid the identification of the infecting organism, Toms *et al* [30] proposed a classification consisting of four modes of presentation of PJI as follows:

Stage 1: acute infections occurring within 6 wk

Stage 2: Late onset with a chronic indolent infection

Stage 3: Sudden onset in an otherwise well-functioning prosthesis with an acute presentation of infection secondary to hematogenous spread

Stage 4 proposed by Tsukayama, Estrada, and Gustilo: [31] When a positive culture is found at the time of surgery without previous evidence of infection.

Pathophysiology of periprosthetic joint infection

Most PJI cases are iatrogenic due to inoculation of micro-organisms intraoperatively.[13] Based on the virulence of the infecting microorganisms, PJI could either has an early presentation (during the first 4-6 wk postoperative) or be delayed (usually three months to three years). Early infections usually present with distinct local and systemic signs of inflammation and are typically brought on by highly virulent microorganisms (e.g. *Staphylococcus aureus, Streptococci, Enterococci*). On the other hand, low-virulent organisms (e.g. coagulase-negative *Staphylococci* or *Cutibacterium* species) are the culprits of the delayed infections, which usually present with milder signs. [2,13] [Figure 1] The presence of foreign bodies, such as orthopedic implants, increase the infection risk brought on by the establishment of the so-called biofilm. [32] The course in which a biofilm is formed consists of several steps: adherence of the microorganisms to the implant, multiplication and elaboration of exopolysaccharides ("glycocalyx") and with time microcolonies encased in glycocalyx coalesce to form the biofilm. [33] Near the biofilm's surface, microorganisms are generally metabolically active and have access to nutrients. On the other hand, deep within the biofilm, microorganisms receive far less supplies and therefore become metabolically inactive or in different states of dormancy which make them immune to host defenses. [34] Hence, antimicrobial therapies may be negatively impacted by the microenvironment within a biofilm as the diffusion through the biofilm may be limited.[33] Due to the high vascularity of periprosthetic tissue, all implants are at high risk of hematogenous seeding from a distant primary focus during their entire indwelling time. However, the highest risk of hematogenous infection occurs in the first few years after implantation. [2,35]

Treatment plan

Management of PJIs remains controversial and therefore, treatment plans should be tailored for each patient individually. Eradication of the infection, reduction of the pain and restoration of joint function are the primary goals of treatment. [12] In general, management of PJI consists of antimicrobial therapy alone or antimicrobial therapy combined with single or staged surgeries. The approach depends on several factors including the timing and microbiology of infection, condition of the joint and implant and individual patient circumstances. Surgical options include debridement and retention of the prosthesis, resection arthroplasty with reimplantation in a single or staged procedures, resection arthroplasty alone as a definitive solution or in extreme situations amputation. [36] Two-stage revision remains the favorite surgical option with overall higher rates of eradicating PJIs in comparison to the single-stage revision. For example, Elson *et al* [37] reported 3.5% failure rates with the two stage revision *vs* 12.4% using a single-stage strategy. Similarly, Garvin *et al* [38] reported a failure rate of 5.6% *vs* 10.1%, respectively.

For the purpose of this review article, we will focus mainly on the two-stage revision method.

Two-stage revision

The two-stage revision procedure is considered to be the gold standard for the management of PJIs. [12] It was described in 1983 by Insall *et al.* [39] and in 1995, Garvin and Hanssen [40] conducted a literature review which showed the great success associated with this approach. The first stage of the procedure includes the removal of the in-situ prosthesis, thorough debridement of the infected bone and soft tissues and the implantation of antibiotic-loaded cement (ALC) spacers for temporary fixation. The interim period between the two stages includes administration of intravenous antibiotics and close monitoring of the patient clinically and serologically for resolution of infection. Once the infection has resolved, the second stage is completed and this includes the use of antibiotic-loaded cement for reimplantation of the definitive

prosthesis. [12,41] The time between stages can be anywhere from six weeks to several months. Both stages necessitate aggressive debridement of all infected and necrotic tissues. [41]

Indications for two-stage revision

The following provide indications for using a two rather than a single-stage revision procedure: [12]

Systemic infection (sepsis)

Clinically convincing signs of infection, but inability to identify the causative microorganism

Antibiotic-resistant microorganisms identified by preoperative cultures

Presence of a sinus tract

Insufficient soft tissue coverage to allow single-stage procedure

1st Stage

The first stage entails a thorough and vigorous debridement of the whole effective joint space after the removal of all implanted materials and cement. [41] [Figure 2] Whenever possible, the use of antibiotics is postponed until all microbiological samples have been collected. To increase the likelihood of receiving a conclusive diagnosis, it is recommended to send for aerobic and anaerobic cultures at least three and as many as six intraoperative periprosthetic tissue samples or the explanted prosthesis itself. [42] The sensitivity, specificity, positive predictive value, and negative predictive value with a minimum of two positive samples have been reported to be 94%, 97%, 77%, and 99.9%, respectively,. [43] It is advised to excise the old scar and the sinus tract if present. Sending the prosthetic parts for sonification is an option but this should be planned prior to surgery as it requires special packaging. [41] It is crucial to remove any cement, even if it is firmly affixed to the underlying bone, in addition to any soft tissues that are grossly involved in the infection process. [44] Osteotomes, specialized chisels, drills, and

taps, as well as various methods that make use of ultrasound-based extraction instruments, can all be used to remove the cement. [45] During this stage, the surgeon must proceed cautiously since iatrogenic bone injury is a possibility. [44] [Figure 3] It is important to perform extensive lavage with a high-pressure pulsatile lavage system using at least 6 Liters of fluid. Normal saline is usually favored. This provides a significant mechanical action that eliminates sequestra, necrotic tissue, microorganisms and dilution. Several publications have looked into adding antibiotics to the normal saline, but no therapeutic advantage over plain lavage solution has been shown. [41] Following the removal of the implants and thorough debridement, new sterile drapes are applied followed by a spacer with ALC. [Figure 4 and 5] Spacers are either static or dynamic, prefabricated or handcrafted and hemiarthroplasty spacers can replace both sides of the joint. Preoperative culture and sensitivity of the infecting microorganism(s) help deciding on the best antibiotics to be added preoperatively to the cement used for construction of the spacer. A discussion with a microbiologist is also necessary to agree on the best choice of antibiotics. [41]

Interim period

At this point, antibiotic therapy is the cornerstone and should be tailored depending on the microorganism's antimicrobial sensitivity. With the help of a microbiologist, empiric therapy should be started if the organism or sensitivities are unknown until those are discovered. To identify an organism, all reasonable efforts should be made. [41] The most popular regimen is intravenous (IV) antibiotics for 4-6 wk followed by discontinuation of the antibiotics for a period of 2-8 wk prior to the second stage as this regimen results in a high rate of infection control. [46,47] The best results are usually obtained when the infecting microorganism is sensitive and systemic antibiotics are used concomitantly in the interim period. [48,49] Prolonging the interim period has been linked with suboptimal infection control rates and function restoration of patients. [12] However, a single study concluded that there were no differences in functional outcomes between patients who had undergone a two-stage revision with an interim period of less *vs* more than 6 mo

between resection and reimplantation. [12,19] Deciding to move forward with prosthesis reimplantation depends on clinical, serological and joint aspirate assessment. Residual infection requires further debridement and a new spacer insertion. [41] Normalization of the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) alone does not guarantee eradication of the infection, especially in coagulase-negative staphylococcal infections as those may not trigger a significant inflammatory response in the first place. [12] Kusuma *et al* [50] reported that synovial white blood cell (WBC) count is the most reliable predictor of infection control and a decision to proceed to the second stage depends on attaining less than 3,000 WBCs/microlitre with a differential of less than 80% polymorphonuclear (PMN) cells from the joint aspirate. Negative intraoperative frozen sections and tissues appearing noninfected are other criteria which they utilise at the time of the second stage to support the decision of proceeding with reimplantation as culturing the joint fluid preoperatively carries a high risk of false positive and negative results and hence a joint aspirate is mainly used for cell count assessment. [50]

Spacer

Spacers are categorized as articulating (dynamic) and non-articulating (static) spacers. Between staged procedures, dynamic spacers maintain ambulation and joint range of motion which protects against muscle wasting and evidence has shown them being as efficient in eliminating infection as static spacers. [51] Being able to maintain a range of motion also prevents against the formation of soft tissue and muscles contractures which facilitates the reimplantation procedure. [12,52,53] Brunnekreef *et al* [54] found a better and quicker recovery of knee function with dynamic spacers, resulting in shorter operation times. Furthermore, compared to static spacers, the use of a dynamic spacer appears to increase the rate of infection eradication (91.2% *vs* 87%) [55] Moreover, using a static spacer may result in bone loss due to migration of the spacer. [56,57] Despite the above, static spacers may be preferrable in certain circumstances such as massive bony and soft tissues loss, ligament laxity in the knee and deficiency of the abductors muscles in the hips. [41,44] Prosthesis with Antibiotic-Loaded Acrylic Cement (PROSTALAC) is an

example of an articulating spacer that delivers high concentration of broad-spectrum antibiotics locally. A common regimen used in PROSTALACs is the inclusion of 3 g of vancomycin and 2 g of gentamicin in each sachet of Palacos R cement (Schering Plough Ltd, Labo nv, Belgium). However, antibiotics in spacers may also be prepared according to the sensitivities of the infecting micro-organisms if detected preoperatively. [12] Spacers are usually augmented with a post-operative course of intravenous antibiotics until the definitive antibiotic sensitivities of the infective micro-organisms are detected from the intraoperative cultures taken at the first stage procedure. [12] Spacers are not complications-free. Faschingbauer *et al* [58] reported that out of 138 patients, 27 (19.6%) developed complications including spacer fractures in 12 cases (8.7%), dislocation in 12 cases (8.7%), a case of a periprosthetic femoral fracture with a spacer in situ, another which had a dislocation with simultaneous spacer fracture and a case of protrusion into the pelvis.

2nd Stage

The second stage consists of removal of the spacer, further debridement, and collection of tissue samples then definitive reimplantation of the new prosthesis. [Figure 6] The decision to proceed with the definitive reimplantation must be made after the resolution of all infection-related symptoms and signs and improvement of laboratory results (a declining trend of CRP and ESR may be accepted as opposed to complete normalization of the values as stated earlier). [41,44] During the second stage, the same old scar is usually utilized to approach the joint. [59] Once the joint is appropriately exposed, further samples are obtained for cultures. It is crucial to remove the cement spacer with its pseudo-synovial cavity that had developed around the spacer without compromising the surrounding bone. Necrotic tissues are removed, and pulse lavage is used for extensive irrigation of the joint. This ensures the removal of any residual cement debris which may become a cause for third body wear in the future. If necessary, bone allografts may be utilized at this point to reconstruct any bony deficiencies followed by reimplantation of the definitive prosthesis in accordance with the preoperative plan. The use of bone allografts in revision surgery

after PJIs has drawn some controversy in the past. [60] Latest evidence, however, has not been able to demonstrate a substantial difference in the rates of re-infection following the use of allografts in this context. Therefore, when there is considerable bone loss, bone grafts may still be used safely. [61] Both cemented and uncemented prostheses may be utilized for the definitive implants. Modern antibiotic delivery methods like DAC (Defensive Antibacterial Coating) may also be utilized at this stage. [62] Similar re-infection rates and aseptic loosening have been reported when using cemented and uncemented prostheses in TKR revisions for infection. [63] Following surgery, antibiotics may be administered until the bacteriology results are revealed. [12] If any suspicion remains regarding infection during the second stage, a synovial leucocyte esterase strip test, synovial alpha-defensin and/or a frozen section may be used to confirm this intra-operatively. If the tests are suggestive of residual infection, aggressive debridement followed by a cemented spacer reimplantation (a repetition of the first stage) is necessary. [41,44] [Figure 7]

CONCLUSION

PJIs are challenging to manage but recent advancements in laboratory tests have helped to facilitate early diagnoses when used collectively under the internationally agreed definition for infections. A multi-disciplinary team approach is crucial when dealing with such cases. Efforts should be made to diagnose the causative microorganism as early as possible to start appropriate antimicrobial therapy and plan surgical intervention accordingly. In terms of surgical options, the two-stage revision procedure remains the gold standard approach in chronic cases yielding the highest eradication rates.

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