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REVIEW

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A review of current practices in periprosthetic joint infection debridement and revision arthroplasty

Humza M. Mian^{1*}, Joseph G. Lyons¹, Joshua Perrin², Andrew W. Froehle^{1,3} and Anil B. Krishnamurthy¹

Abstract

Background: Periprosthetic joint infection remains a significant challenge for arthroplasty surgeons globally. Over the last few decades, there has been much advancement in terms of treatment and diagnosis, however, the fight rages on. As management of periprosthetic joint infections continues to evolve, it is critical to reflect back on current debridement practices to establish common ground as well as identify areas for future research and improvement.

Body: In order to understand the debridement techniques of periprosthetic joint infections, one must also understand how to diagnose a periprosthetic joint infection. Multiple definitions have been elucidated over the years with no single consensus established but rather sets of criteria. Once a diagnosis has been established the decision of debridement method becomes whether to proceed with single vs two-stage revision based on the probability of infection as well as individual patient factors. After much study, two-stage revision has emerged as the gold standard in the management of periprosthetic infections but single-stage remains prominent with further and further research.

Conclusion: Despite decades of data, there is no single treatment algorithm for periprosthetic joint infections and subsequent debridement technique. Our review touches on the goals of debridement while providing a perspective as to diagnosis and the particulars of how intraoperative factors such as intraarticular irrigation can play pivotal roles in infection eradication. By providing a perspective on current debridement practices, we hope to encourage future study and debate on how to address periprosthetic joint infections best.

Keywords: Prosthesis-related infections/prevention & control, Prosthesis-related infections/surgery, Debridement, Anti-bacterial agents, Arthroplasty, Biofilms, Knee prosthesis, Hip prosthesis, Orthopedic surgeons

Background

Periprosthetic joint infections (PJI) continue to be one of the most significant challenges facing arthroplasty surgeons today. Current data estimate the risk of PJI at approximately 2% [1–3] after primary procedure and as high as 15% [4–7] after revision procedures, which has led us to over a billion dollars in healthcare spending annually in managing PJI [8]. Our aim through this

perspective is to address and review current concepts in PJI debridement. In order to understand the role debridement plays in PJI, we first discuss criteria for PJI diagnosis. As such, we will review several viewpoints regarding the role of debridement in PJI: diagnosis of PJI, role of intra-articular irrigation, debridement, and antibiotic implant retention (DAIR), one-stage revision, and the gold standard being two-stage revision. Considering the morbidity posed by PJI and the ever-increasing number of arthroplasty procedures performed annually, reviewing treatment of PJI remains as critical as ever to ensuring optimal quality of life for patients whose only goal is to minimize sometimes decades worth of arthritic pain.

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Main text

Diagnosis of periprosthetic joint infection

In this section, we will discuss the evolution of relevant diagnostic criteria that guide orthopedic surgeons across the world in diagnosing PJI. While multiple definitions for PJI have been suggested, there remains no universally accepted definition for PJI. In 2011, the Musculoskeletal Infection Society (MSIS) convened and set forth a set of criteria to assist in diagnosing PJI. The criteria are divided into major and minor criteria respectively. The major criteria include the following: presence of a sinus tract communicating directly with the prosthesis, or a single pathogen grown on culture based on a minimum of two distinct aspirates or tissue specimens from the joint in question. Presence of either of these criteria would, according to the 2011 MSIS definition, indicate presence of a periprosthetic joint infection. In the absence of either major criterion, the society recommends the presence of at least 4 of 6 minor criteria which include the following: elevated leukocyte count, elevated serum C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), elevated neutrophil percentage isolated from synovial fluid, gross purulence within the suspected joint, the positive isolation of one pathogen in a single culture or sample of periprosthetic synovial fluid, or finally more than five neutrophils identified on a high-powered microscopic field from five distinct fields seen on periprosthetic tissue histology [9, 10]. These criteria were externally validated in a multicenter study published seven years later that included upwards of 1500 patients. In this cohort study, elevations in serum CRP and ESR were the two most predictive variables associated with PJI [11].

Two years after the MSIS definition was developed, a conference of some 400 delegates from over 50 countries convened in Philadelphia to reassess the MSIS criteria ahead of the annual MSIS meeting. This meeting came to be known as the International Consensus Meeting on Periprosthetic Joint Infection (ICM). Based on their collective wisdom and review of the available literature, the group decided to include pathologically-elevated leukocyte esterase values as an additional minor criterion [12–14]. While leukocyte esterase had been discussed earlier at the 2011 MSIS meeting, there was concern about the reliability of the test in part due to concerns regarding different reagents and testing materials. Controversy surrounding the inclusion of leukocyte esterase revolves around the confounding effect that blood can have on reading the results as documented in a prospective cohort study conducted at two centers. The study evaluated the limitations of leukocyte esterase reagent (LCR) strips. They can be deemed indecipherable due to colorimetric nature of the strip pad, which simultaneously

introduces human error, by way of subjectivity, into the equation as well [15–17]. In addition, there has been significant discussion concerning other reagents playing a role in the diagnosis of PJI, such as alpha defensin or D Dimer [11, 18]. With the addition of leukocyte esterase, there was an increase in sensitivity of diagnosing PJI, with a small decrease from around 98% to 95% in specificity [17]. Additionally, PCR techniques have been suggested as possible replacements for current serological testing. While there may be a role in the future, multiple studies have demonstrated that PCR testing is not superior, in the diagnosis of PJI, to the already established criteria and can even prove inferior to culture identification. In fact, specificity of PCR-driven diagnosis techniques can be as low as 75%, with a positive predictive value under 40% [19–24].

In 2018, the MSIS conducted the most significant overhaul of the existing PJI criteria to date. They incorporated synovial alpha defensin as a significant minor criterion, which was given a score of 3 points, which was higher than the individual value given to any other minor criteria. Sensitivity and specificity were approximately 98% and over 99% respectively based on external validation, which was higher than previous scoring criteria [18, 25–27]. Later in 2018 and 2019, the definition was given another thorough review by the European Bone and Joint Infection Society (EBJIS) with support from the MSIS, European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Rather than splitting the criteria into major and minor groups, the EBJIS had three distinct groups based on existing clinical and serological markers: infection likely, infection unlikely, or infection confirmed. As in previous definitions, this definition relies on clinical examinations, serological markers such as CRP, leukocyte count with PMN%, alpha defensin, culture results, sonication results, histology, as well as incorporating nuclear imaging. Up to this point, none of the previously discussed criteria incorporated sonication into the diagnosis of PJI. Within the context of PJI, sonication is the targeting of bacterial biofilms with sound waves to disrupt or dislodge pathogenic bacteria. This would, in turn, increase the likelihood of resulting positive cultures and therefore diagnosing a PJI. This technology has been externally validated at length, demonstrating its utility in diagnosis. In 2007, a large prospective trial demonstrated an almost 18% increase in sensitivity in diagnosing PJI when using sonicated periprosthetic joint tissue *vs.* without. The same trial also found the gap in sensitivity to significantly widen to 35% when evaluating patients on antibiotic therapy [21, 28]. While specificities were comparable with less than a 1% difference, the stark divide in sensitivity highlights the important role sonication can play. While this study demonstrated overwhelmingly the

benefits of sonication in diagnosing PJI, there has been supporting literature indicating that using sonication on arthroplasty implants can increase the likelihood of tissue culture positivity, increasing sensitivity of PJI diagnosis [28–32]. Despite the value of sonication technology as previously mentioned, it has yet to be incorporated into any diagnostic criteria outside the recent EBJIS definition. In turn, the EBJIS diagnostic criteria have yet to be externally validated in a meaningful study. Overall, definitions and criteria continue to be revised and augmented with the study of new and emerging technologies that can help guide us toward a universally-accepted set of criteria for PJI diagnosis. Some of these new technologies aimed at addressing biofilms include the following: cathodic voltage controlled electrical stimulation, electrochemical scaffolds, hyperthermia, polyclonal antibodies, antimicrobial peptides, and endogenous molecules such as bacteriophages [33–35]. A complete discussion of each of these technologies and their respective efficacy falls outside the scope of this paper, however, it is crucial to keep molecular level treatments in mind as we focus on the macromolecular treatments offered through standard revision arthroplasty and the debridement techniques which are the focus of this paper.

Treatment of PJI

Role of intra-articular irrigation

In the past decade alone, there has been much debate as to which antiseptic or antibacterial solution is superior in treating PJI. However, what is not debated is the role that intra-articular irrigation plays and its importance in treating PJI. Most can agree that the primary goal of any intra-articular irrigation solution is eradication of the biofilm that leads to such a high reinfection rate and eventually multiple revision surgeries [36, 37]. As biofilm is the primary target of any debridement technique, we should briefly review the concept itself. Biofilms have been suggested as the most critical factor influencing PJI treatment. Biofilms essentially are formed by any bacteria and occur on foreign surfaces such as implants. The threat posed by biofilms lies in their inherent ability to generate a microcosm of pathogenic growth shielded from conventional antibiotic delivery systems. Oftentimes, bacteria protected by biofilms can multiply their resistance to antibiotics upwards of 1000 times. Failure to address the biofilm ensures recurrence of infection in short order, highlighting the importance of proper debridement [38–42].

Staphylococcus species has long been known to cause PJI. *S. epidermidis* and is the most common offending agent and forms sturdy biofilms on implanted structures [43, 44]. *S. aureus* is another species that has been shown to be an independent risk factor for treatment failure,

most likely due to its penchant for antibiotic resistance [44–47]. *S. aureus* has also been shown to be the leading cause of hematogenous total knee arthroplasty infections, which are less receptive to treatment [48, 49]. Based on these concerning findings, *S. aureus* has been the target of many studies.

Much of the current literature reviewing intra-articular irrigation focuses on *in vitro* studies. In fact, one study compared commercially-available solutions including Bactisure (Zimmer Biomet, Warsaw, IN, USA) and Irrisept (Irrimax, Gainseville, FL, USA) against diluted betadine and sodium chloride solutions. These solutions were tested against strains of *S. aureus* and *S. epidermidis*. During this *in vitro* study, media treated with Irrisept were found to have the highest statistically significant remaining colonies of all bacterial strains when compared to other solutions. Betadine and Bactisure, which is a combination of water, sodium acetate, benzalkonium chloride, acetic acid, and ethanol, were comparable in their efficacy in eradicating bacterial biofilms [50, 51].

Furthermore, studies have evaluated the role of antibiotic-supplemented solutions. For example, vancomycin combined with povidone solutions when compared to povidone alone in a large retrospective cohort looking at over 11,000 patients did demonstrate relative reduction in infection risk but no significant difference was found when it came to PJI incidence [52]. Besides vancomycin, gentamicin has also been evaluated as an adjunct to irrigating solutions, with similar findings suggesting that antibiotic supplementation may not be as beneficial as one would imagine [53]. A polymyxin and bacitracin irrigation solution has similarly been tried and demonstrated as inferior to betadine solution in eradicating biofilms [54]. In a randomized controlled trial published in 2020, betadine solution was compared to saline lavage and there was, in fact, a difference in the number of postoperative infections. There was a significant decrease in the number of postoperative infections in the group utilizing the betadine lavage over the saline lavage [55].

The ongoing debate as to whether solutions such as betadine are superior to chlorhexidine gluconate-based solutions illustrates the useful adjunct that intra-articular irrigation plays. In choosing which solution is superior, most agree that it should be capable of penetrating the biofilm that is a hallmark of chronic PJI, while remaining minimally-cytotoxic to host tissue that will prove crucial towards the inevitable lengthy healing process [56–59]. In addition to the contents of the irrigating solution, there has been significant discussion regarding appropriate irrigation pressure and duration. Multiple studies have compared high pressure lavage vs. low pressure lavage, with the majority of available literature corroborating the effectiveness of low pressure lavage in favor of

high pressure lavage [60–64]. When discussing duration of irrigation, an *in vitro* study demonstrated that bacteria must be exposed to a minimum of 120 seconds of irrigation using commonly available irrigation solutions such as, but not limited to, povidone, chlorhexidine, and acetic acid based solutions [65].

One-stage and DAIR

One-stage revision arthroplasty or single-stage revision (SSR) has been gaining favor amongst orthopedists in recent years due to decreased mortality, comparable infection eradication rates, and lowered cost when compared to two-stage revision arthroplasty procedures [66–69]. The first step in a one-stage revision protocol is to achieve adequate exposure to the affected area. Once exposed, local excision of skin margins, synovium, and any sinus tracts is performed similar to any other debridement procedure. All implants are then removed, and then copious irrigation follows. After the surgeon has appropriately debrided, removed the implants, and then irrigated the infected joint, the new implants are then placed. Most often, the cement used during the revision procedure is impregnated with antibiotics.

Indications for a single-stage revision arthroplasty (SSR) currently remain broad and ill-defined, however, they continue to evolve. In one study, patients were eligible for one-stage revision if they had symptoms lasting longer than 4 weeks and did not have systemic symptoms, extensive soft tissue involvement that would prevent wound closure, fungal infection, HIV infection, or they were on chemotherapy [70]. In another review article comparing one- and two-stage revision arthroplasty, it was determined that relative indications for one-stage revision over two-stage were an affected THA, good soft tissue, appropriately identified organism with susceptibility to oral agents, good bone stock, and no bone grafting required [69]. These indications for one-stage revision are substantiated by a consensus article published in the *Journal of Orthopaedic Research* in 2014. In the article, it was determined that indications for one-stage revision arthroplasty included circumstances where effective antibiotics were available but did not include patients with systemic manifestations of infection [71]. In terms of the evolution of single stage revision, there has been significant advancement in recent years. One of the hallmarks of the new set of indications is the need for proper identification of the offending microbe with appropriate sensitivity and resistance testing completed prior to initial debridement. Knowing what organism is most likely responsible has significant impact on the likelihood of success of SSR and, as such, has become a major indication for SSR if this knowledge is available [72, 73]. Armed with this knowledge, the operating surgeon is

able to select the appropriate antibiotic to load into the cement for the revision as well as optimize the postoperative antibiotic plan to ensure the best chance of success [74, 75]. In the past, relative indications to proceed have relied on the absence of gross signs of infection or instability such as radiographic loosening, radiographic signs of osseous inflammation, and grossly draining sinus tracts [76–79]. In one clinical study, WBC, CRP, and joint aspirate results were not associated with treatment failure. However, identification of *Streptococcus* species was conversely associated with treatment success. Additionally, elevated ESR values above approximately 47 mm/h were associated with treatment failure, suggestive of more deep-seated and chronic infections not amenable to SSR [76]. Body mass index, which has been historically associated with high risk for infection after primary arthroplasty, may have a role to play in determining success of SSR as well. While not well borne out in the literature there were some data to suggest that higher BMI is associated with failure of SSR [80]. Ultimately, outcomes in terms of treatment success for SSR have a wide range of little clinical significance stretching from less than 20% to above 80% in current literature [81–85]. Relative contraindications for one-stage revision were voted to be lack of identification of an organism preoperatively, the presence of a sinus tract, or severe soft tissue involvement that may lead to the need for flap coverage [71]. More research needs to be done in order to come to a consensus on what criteria best justify a one-stage revision.

We also discuss debridement, antibiotics, and implant retention (DAIR) in this section as it is similar in scope to a one-stage revision. DAIR is a surgical procedure that is often utilized as an alternative to one- and two-stage revision arthroplasty to treat prosthetic joint infection (PJI). When compared to revision arthroplasty, DAIR has been associated with superior functional outcomes due to its ability to minimize bone loss and soft tissue trauma [86, 87]. There is also a reduced risk of intraoperative fracture due to implant retention, and overall procedure times are shorter on average [88, 89]. Some studies even reported faster postoperative rehabilitation when compared to other revision procedures [90]. However, DAIR is not without its drawbacks. Unlike one- and two-stage revisions, DAIR protocols reported variable infection cure rates [91–93]. Additionally, the success of DAIR is questionable in scenarios such as the presence of hip fracture [94, 95]. In the following paragraphs we discuss some of the current concepts regarding debridement, antibiotics, and implant retention.

Indications to perform a DAIR procedure are not rigidly defined. It has been suggested that a short duration of infection in a non-immunocompromised host

with identified and antibiotic-sensitive organisms are relative indications for a DAIR procedure [96]. Relative contraindications to DAIR include chronic infection, infection with multi-drug-resistant organisms, polymicrobial infections, and fungal organisms [97, 98]. The steps in a DAIR procedure are similar to a one-stage revision, except the implants are never removed. Modular components, such as the plastic spacer, may be removed to improve visibility of the posterior capsule or even exchanged, but the remaining structures are not removed. Because the components are left intact, it is vital to perform extensive debridement and thorough irrigation, most often with 6–9 liters of normal saline. There is increasing support for irrigating the infected joint with antiseptic solutions, such as chlorhexidine and betadine, as previously discussed. Both solutions have been shown to prevent postoperative infection after arthroplasty [55, 99] and have yielded similar results when used with revision arthroplasty [55]. Some orthopedic surgeons have adopted this practice and have been utilizing antiseptic solutions in their DAIR protocols with success [100, 101].

Pulse lavage is another irrigation technique that can be used with a DAIR protocol. In one study, pulsed lavage achieved a 94% 2-year survival rate free of treatment failure [102]. Despite this promising outcome, pulsed lavage has not been proven superior to standard lavage techniques in other studies [103]. Once debridement, irrigation, and exchange of modular implant components are completed, the wound is often closed and a suction drain left in place. There is also the option to outfit the patient with a continuous closed irrigation system, however, one study showed continuous irrigation achieved the same infection control as a suction drain, but with the disadvantage of increasing hospital stay time [104]. This makes a strong argument for the use of suction drains.

After surgery, either one-stage revision or DAIR, the patient then undergoes antibiotic treatment. Antibiotics are typically held preoperatively if the pathogen is unknown. In the immediate postoperative period, broad-spectrum antibiotics are started until microbiological results are obtained. Once the pathogen is identified, antibiotic therapy is initiated based on susceptibility profiles. Initially, patients are given intravenous antibiotics for 2–6 weeks following the procedure [83, 90, 92, 105]. After intravenous treatment is completed, many surgeons treat their patients with long-term oral antibiotic therapy to ensure biofilm eradication or suppression [82, 106, 107]. Some surgeons are also utilizing direct intra-articular antibiotics with some promising results [108].

Despite the consensus that patients who undergo a DAIR procedure require long-term antibiotics, the exact duration that they should be treated remains a point of contention. A study by Byren *et al.* in 2009 suggested that

the risk of treatment failure increases 4-fold after the cessation of antibiotics, with most of those failures occurring within 4 months of antibiotic stoppage. In this study, the researchers treated their patients for an average of 1.5 years [82]. On the other hand, some studies suggest a shorter duration of antibiotics: as little as 6 weeks to as long as 6 months are just as effective at treating PJI as a more drawn-out antibiotic course [109–111]. One study even states that the only factor associated with treatment failure in their population was the antibiotic selection and not the duration of treatment [46]. The inability to determine a best practice treatment duration suggests that failure is more complex than we previously thought, and relies heavily on the infecting pathogen and how it relates to a patient's own comorbidities. The latter has the potential to delegate a patient to lifelong antibiotic therapy, which deserves future study.

When it comes to specific antibiotic regimens used in PJI treatment, there has been a movement towards adding rifampin to existing antibiotic regimens when treating *S. aureus* infections. This addition has been shown to be superior to historical cohorts that were not treated with Rifampin [112]. Unfortunately, these results have not easily been replicated. In a randomized controlled trial, rifampin combination therapy did not have any statistically significant advantage over standard antibiotic regimens when treating *S. aureus* PJIs [113]. Becker *et al.* were able to replicate the success with improved outcomes when rifampin was added to standard therapy in their study. They found the primary determinant of treatment success to be the duration of rifampin therapy, with longer duration proving more fruitful [114]. Due to the nature of the organism, there also exist strains that are resistant to rifampin. For these cases, it is recommended to treat the patient with linezolid, as it has been associated with high remission rates and is an appropriate alternative for infections due to fluoroquinolone and/or rifampin-resistant bacteria [115].

As previously mentioned, the treatment success rate of DAIR is highly variable, ranging from approximately 30% to 90% efficacy [83, 116–118]. One factor not previously discussed that can determine the success of a DAIR procedure is early intervention [100]. Performing a DAIR procedure within 4 weeks of infection onset has been associated with superior outcomes than DAIR procedures performed later in the infection's course [119]. Interestingly, one of the factors that has been associated with worse outcomes is the presence of fracture, which decreased treatment success rates [95]. Thus, in patients who have undergone hemiarthroplasty for hip fracture, it is critical to take note of the increased risk of DAIR failure. Though DAIR can have superior outcomes when compared to two-step revision arthroplasty [86], if the

procedure fails, through any means, a second DAIR may be performed. However, the efficacy of the repeated procedure over a revision arthroplasty is a research topic that needs to be expanded upon.

Two-stage revision arthroplasty

Two-stage revision arthroplasty for PJI has long been accepted as the standard against which all other revision procedures are measured [120–123]. This mainly stems from infection cure rates being reported as high as 90% and reinfection rates around 15% [121–124]. It is also easy to overlook the advantage of being able to debride an infected joint twice and treat a patient long-term with interim antibiotics. There is also the benefit of the surgeon having a better understanding of the bony and soft tissue defects a patient may have, a benefit when planning the second surgery. This can be appreciated in the study by Hsieh *et al.* (2005), when 24 patients with massive femoral and acetabular bone loss were successfully treated with two-stage revision. They were initially treated with a temporary cement prosthesis. After a period, definitive treatment came in the form of an endoprosthesis that was cemented into an allograft designed for the bone loss [125].

Just like many other procedures, two-stage revisions are not without their drawbacks. The most obvious argument against this treatment protocol is the fact that the patient must undergo two separate surgeries. Perhaps most importantly, two-stage revision procedures are associated with a high mortality rate [68]. Additionally, two surgeries increase the economic burden on the hospital system. It has been estimated that the combined annual hospital cost of treating PJI with a two-stage procedure may be as high as 1.85 billion USD by 2030 [126]. There is also the concern for resource and staff allocation, especially during the COVID era when resources are often harder to come by and staff are already spread thin. Two surgeries increase the cost directly to the patient when compared to other treatment modalities. A two-stage procedure may cost anywhere from 1.5–1.7 times that of a single-stage revision [66, 67]. Compared to a DAIR protocol, two-stage revision may cost three times as much [127]. There are also hidden costs to the patient such as increased time off from work, transportation costs, increased time being disabled in the interim between surgeries, and there is always the concern for loss to follow-up.

The gap in PJI eradication between two-stage revision and other procedures is closing thanks to modern technology [87, 128]. In a retrospective cohort study assessing patient-reported outcome measures (PROMs) for single *vs.* two-stage revision of chronic infection of

total hip arthroplasty, Tirumala *et al.* demonstrated a functional benefit of one-stage revision when compared to its two-stage counterpart. Both treatment modalities improved PROM scores, however, these scores were significantly higher for one-stage revision THA [129]. Two-stage revision has also undergone changes throughout the years thanks to technological advances. However, the principles of a two-stage revision surgical protocol have remained the same. In the following sections, we discuss the indications and contraindications, what a typical two-stage revision looks like as well as some of the technological advances that have shaped what the procedure has become today.

The indications for a two-stage revision arthroplasty are often not well defined. In a study assessing 253 two-stage revisions for infected TKA, the indications for two-stage surgery were evidence of chronic infection, increased CRP, positive culture report, and/or intraoperative histology consistent with infection [122]. The contraindications, in the same study, were patients with documented infection who were not able to undergo surgery or patients without evidence of infection [122]. In many cases, the indication to perform a two-stage revision is the contraindication to a one-stage one. For example, the signs and symptoms of systemic infection, inadequate tissue coverage, the presence of a sinus tract, and an unidentified infecting pathogen [71, 130].

A two-stage revision arthroplasty for PJI begins with surgically opening the affected joint and removing all implanted materials. The joint is then debrided of all suspicious tissues and debris. After the joint is thoroughly inspected and cultures are obtained, an antibiotic-impregnated spacer is fitted. The joint is then closed. During this interim period, the patient is typically treated with antibiotics, IV, oral, or a combination of both. Once the patient has met certain criteria, the second surgery is done, typically 6–12 weeks later. The antibiotic implant is removed, the joint is thoroughly inspected and debrided once again, and then the patient is outfitted with a new permanent prosthesis.

The antibiotic-impregnated spacer is considered one of the true advantages of a two-stage procedure. The primary goal of the spacer is to stabilize the joint and provide adequate concentrations of antibiotics to the otherwise difficult to penetrate area. Fink *et al.* (2011) wanted to know if antibiotics from a spacer could be detected in the tissues surrounding the spacer 6 weeks after implantation. They had 14 spacers, removed from 14 patients. Half of the spacers were impregnated with gentamicin and clindamycin alone; vancomycin was added to the remaining seven. They were able to detect all three antibiotics in concentrations higher than their minimum inhibitory concentration (MIC) in the

surrounding tissue samples and the membrane that formed between the spacer and the native tissue [131]. These levels of antibiotic concentration for such a duration would be impossible without the use of the spacer.

The antibiotic of choice is typically determined with the help of an infectious disease specialist and pre-surgical joint aspiration microbiological studies [132]. One thing surgeons should keep in mind is the exothermic reaction that occurs when bone cement is curing. Temperatures can reach 82–86 °C (approximately 180 °F), thus it is imperative to choose a heat-stable antibiotic [133]. Once the antibiotic is chosen, the surgeon must decide whether to use a static or mobile spacer. A static spacer can simply be defined as taking up the dead space where the implant used to be and not allowing motion through the knee joint [134]. The joint may be kept in full extension or minimal flexion, at the discretion of the surgeon. There are documented advantages and disadvantages to a static spacer. The primary advantage of a static spacer is the fact that it is an effective therapy at a decreased cost to the patient [135, 136]. The disadvantages of a static spacer are increased stiffness and decreased range of motion (ROM) after the second stage procedure [137]. A meta-analysis by Guild *et al.* (2014) assessed articulating cement and static antibiotic-impregnated spacers. Through 47 studies, there were 1904 patients and 2011 knees. Of those knees, 16 were complicated by arthrodesis, with 13 of those being associated with static spacers [137]. Another meta-analysis by Ding *et al.* (2017), came to similar conclusions [138]. On the other hand, Skwara *et al.* (2016) found no significant change between pre-operative and postoperative ROM in their two cohorts (articulating cement *vs.* static spacer) [139]. On the other hand, decreased ROM observed with static spacers may be a desired trait and may be useful when treating patients with ligamentous compromise or grossly unstable joints.

Articulating cement spacers are also impregnated with antibiotics, but they allow flexion and extension of the knee joint. The immediate advantage of an articulating spacer is improved postoperative ROM [137, 138, 140]. There is also evidence to suggest articulating cement spacers are better at infection eradication [137, 141]. Another possible advantage of articulating spacers is less complex re-implantation procedures. It has been demonstrated that patients with articulating procedures had less complex second surgeries, for example, tibial tubercle osteotomies, than patients with static spacers. The downside to an articulating spacer is a greater cost to the patient [135]. Thankfully, newer technologies, such as 3D printing, may be able to make articulating spacers more affordable. Kong *et al.* (2021) have shown 3D-printed articulating spacers can provide satisfactory ROM with

the added benefit of mitigating bone loss [142]. There is also evidence to suggest pre-fabricated off-the-shelf articulating spacers can achieve comparable outcome measures to more personalized implants [143]. Additionally, we are beginning to see increasing data on the reinfection risk in these antibiotic articulating spacers with one study documenting survivorship free of infection after reimplantation using an antibiotic articulating spacer as over 90% at 2 years and over 85% at 5 years [144]. We can only assume these technologies will continue to be utilized in the coming years to even greater effect.

Perhaps the most controversial and least-studied area of two-stage revision procedures is the interval period. Most surgeons employ a 6–12-week interval period with antibiotics. In the beginning, patients are treated with IV antibiotics and then changed to oral medications. In a study by Hoshino *et al.* (2021), seven patients with PJI were treated with two-stage revision arthroplasty utilizing a hand-made silicone mold in the interim. Also, during the interim period, they were treated with 1 week of IV antibiotics, until laboratory values normalized (CRP, WBC, ESR). They were then treated with 3 months of oral antibiotics. Medications were chosen based on the results of microbiological studies. In this scenario, no incidence of reinfection occurred [145]. In a separate study by Burastero *et al.* (2020), 253 patients treated for PJI with two-stage revision were assessed. The reinfection rate was 4.7%. In this protocol, patients were treated with IV antibiotics routinely for 4 weeks, followed by oral antibiotics for 2 weeks, and then a washout period of 2 weeks prior to the second stage screening for infection [146]. A study by Hsieh *et al.*, (2009) may help explain why both protocols, despite their differences, work. To determine the optimal duration of systemic antibiotic therapy, 99 patients with PJI who were treated with two-stage arthroplasty were split into two groups. The first group was given 4–6 weeks of antibiotic treatment. The second group was put on 1 week of antibiotic therapy. In the end, the short-term therapy was not associated with higher rates of treatment failure [147]. The results of this study suggest treatment success is not dependent on systemic antibiotic therapy during the interval period. In the most interesting case by Stockley *et al.* (2008), no systemic antibiotics were used at all. These researchers treated 114 patients for PJI using antibiotic-loaded cement with no systemic therapy during the interim. They were able to successfully eradicate infection in 87.7% of their patients [148]. The results strongly suggest that systemic antibiotics are not an essential part of a two-stage revision. Understanding important aspects of the interval period, such as how long it should be, what antibiotics should be used (if any), and when we know a patient is ready for it to be over, are all areas that further research needs to

focus on. Ultimately, when it comes to outcomes, differences in infection rates may not be as dissimilar as some would think. In fact, data from one meta-analysis from the *European Journal of Epidemiology* looking at almost 100 studies to identify differences in reinfection rates between one-stage and two-stage revisions, surprisingly, pointed to no statistically significant difference in infection rates [79]. This alone suggests that further research is necessary to identify benefits of one-stage vs. two-stage procedures.

Over the course of this review, we have provided a perspective of PJI diagnosis and treatment, highlighting current practices. Eradication of the biofilm that develops on arthroplasty implants is one of the hallmarks in treatment and the debridement practices described above aim to do just that. Single-stage debridement can play a role in select situations as definitive management for PJI, but two-stage revision is the preferred method in more cases based on the results we have noted. Ultimately, treatment of periprosthetic joint infections will continue to evolve with the constant evolution of antibiotic resistance weighed against our future study and debridement technique evolution.

Abbreviations

PJI: Periprosthetic joint infection; DAIR: Debridement antibiotics and implant retention; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; PCR: Polymerase chain reaction; MSIS: Musculoskeletal Infection Society; ICM: International Consensus Meeting on Periprosthetic Joint Infection; EBJS: European Bone and Joint Infection Society; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; LCR: Leukocyte esterase reagent strips.

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