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Treatment and Prevention of Hospital Infections (D Vilar-Compte, Section Editor)

What's New in the Diagnosis and Treatment of Orthopedic Prostheses-Related Infections

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Opinion statement

Periprosthetic joint infection (PJI) is one of the leading cause of failure in prosthetic joint surgery regardless the implantation site, causing an important burden to hospitals and society. Diagnosis is challenging, as there is lack of a gold standard test. When it is diagnosed within 30 days of onset or if the etiology is hematogenous with either a susceptible or non-virulent microorganism, the recommended surgical management option is debridement and irrigation, followed with antimicrobial treatment in order to preserve the device, with different reported success rates. In those cases of delayed and late onset presentation, there are two treatment possibilities: (a) Two-stage exchange arthroplasty, the most common surgical procedure for the management of PJI. Once prosthesis is removed it is followed by pathogen-specific antimicrobial treatment. A period of 2–4 weeks without antimicrobial before reimplantation procedure is suggested. (b) One-stage exchange arthroplasty is considered in case of a known microorganism that is susceptible with effective antimicrobial options and lack of sepsis. In terms of antimicrobial treatment, length of intravenous antibiotics is at surgeon's discretion because there is not a standard recommendation. Switching from intravenous to oral antimicrobial treatment reduces the hospital length of stay and health-care expenditures. Oral antimicrobial treatment length recommendation is variable, which can be from 2 to 6 weeks to 3–6 months. Suppressive antimicrobials for a long-term are an option when prostheses retention is decided because there is a high surgical risk, poor functional outcomes, and

patient preferences. PJIs are ideally treated in referral hospitals with an experienced multidisciplinary team.

Introduction

The number of total joint arthroplasty (TJA) procedures has increased remarkably as it has been considered a life-enhancing procedure, performing an estimated 770,000 arthroplasty surgeries per year in the United States of America and a projected 4 million TJAs in the year 2030 [1, 2]. TJA is a successful procedure that improves the quality of life and function of patients affected in diverse chronic articular diseases. The vast majority of joint arthroplasties commit their goal of providing pain-free function; but a less amount of patients will require additional surgery for different device problems [3••]. Aseptic complications include loosening at the bone-cement interface, prosthetic or periprosthetic fracture, fatigue, implant malposition, dislocation or deterioration. PJI is defined as infection involving the joint prostheses and adjacent tissue. Infection is the second most common complication after cardiovascular complications, occurring in approximately 1–2% of cases in knee arthroplasties every year and around 1% for hip arthroplasties [4]. The incidence of infection is even higher in revision arthroplasties accounting for 14 and 25% in hip and knee arthroplasties, respectively [1, 5]. These infections can result in increased patient morbidity and mortality. The average costs of one- and two-stage exchanges are 3.4 and 6 times higher, respectively, than the cost of primary implantation [6].

A useful classification of PJI is based on the time of infection presentation, classified as early when it presents from zero to 3 months after the implantation surgery; delayed-onset after 3 months but before 12 to 24 months, and late-onset occurring from 12 to 24 months after surgery [7] (Fig. 1).

Biofilms play an important role in all device chronic infections [9]. They are bacterial communities formed on surfaces and inserted within an extracellular matrix made out of proteins, polysaccharide, and DNA. Protection from antimicrobials and the host immune system are the most important goals for this biological shield [9, 10]. Removing biofilm burden with surgery and adding antimicrobial against its formation are mandatory to increase success rates, taking into account the biochemical characteristics of each biofilm producer bacteria [11]. Biofilms also play an important role to diagnose PJIs, impeding to know the microbiological etiology in most cases until the device is removed and sonicated [12].

The optimal treatment of PJI includes surgical intervention and antimicrobial therapy. Successful treatment is higher when a multidisciplinary team exists including orthopedic surgeons, infectious disease physicians, and nursing and rehabilitation staff involved in the care of the patient. The cornerstone of successful treatment is early diagnosis, the earlier the diagnosis, the less invasive is the surgical therapy. The treatment goals of PJI are to eradicate infection, recover infected joint functionality without pain, and decrease morbidity and mortality associated with the PJI treatment [3••]. When it is not possible, a palliative approach must be chosen, which focus on suppression of infection, and hence of symptoms, requiring only minor or no surgery [2]. There are different surgical approaches to treat PJIs, including

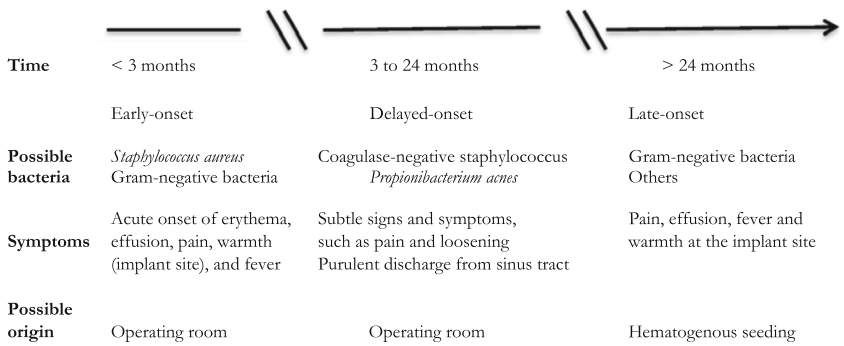

Fig. 1. Prosthetic joint infection classification according to time presentation and its association with other variables. [Modified from 7, 8]

debridement, antibiotic and implant retention (DAIR), resection of the prostheses with reimplantation of a new one, either at the time of removal (one-stage arthroplasty) or delayed by weeks to months (two-stage arthroplasty), resection of the prostheses without reimplantation, arthrodesis, amputation, or antimicrobial suppression without surgery [13••]. Each specific treatment should be chosen for every patient taking multiple variables into account, such as time of implantation, age, causing microorganism and patient's desire [14].

Diagnosis

Diagnosis of PJI is based on the symptomatology, laboratory results, either peripheral blood and/or synovial fluid, microbiological data from multiple periprosthetic samples, histological evaluation, and radiographic results [8, 13••]. The diagnosis needs to take all these components into consideration because there is not 100% accurate test to diagnose PJI. In the last years, an important breakthrough has been the diagnostic criteria from different groups that do help to identify those infected patients (Table 1). Although there are some differences between the required criteria numbers to each group, they agree that a sinus tract communicating with the device and the isolation of the same microorganism in two samples supports PJI [8, 15, 16•].

Laboratory blood tests

The most used peripheral blood tests are the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [17]. Barberi et al. showed in a meta-analysis that the pooled sensitivity and specificity was 75 and 70% for the former versus 88 and 74% for the latter [18]. The common used thresholds are >100 mg/dL of CRP in acute infection, and 10 mg/dL in delayed and late-onset presentation [8].

Interleukin-6 and procalcitonin are recently added studies in some centers for helping infection diagnosis for different diseases; however, there is lack of strong evidence to routinely recommend this test [19••].

Table 1. Periprosthetic joint infection diagnostic criteria. [3••, 8]

Type of information	Criterion
Surgery	Sinus tract communicating with the prostheses* Purulence surrounding the prostheses*
Microbiology	Identical microorganisms isolated in 2 or more cultures* Single culture with any microorganism Single culture with a virulent microorganism
Laboratory	Elevated synovial fluid leukocyte count (>10000 cell/μL–delayed/late) Elevated synovial fluid neutrophil percentage (>90%) Elevated serum CRP values or ESR
Histopathology	Acute inflammation (presence of ≥5 neutrophils per high-powered field, in 5 separate microscopic fields)

CRP C-reactive protein. *ESR* erythrocyte sedimentation rate.
*The diagnosis can be made when one of these criteria is present or when three of the others are met.

Synovial fluid and tissue cultures evaluation

Arthrocentesis is a useful approach to help PJI diagnosis that can be performed either pre or intra-operatively. Neutrophil enzyme esterase detection in synovial fluid may be a useful adjunctive test intra-operatively when infection is suspected with a sensitivity of 81% and specificity of 100% [20], and it has been included recently as a supporting criterion [8]. Caution must be advised when bloody joint is aspirated, suggesting to centrifuge the sample [21]. Synovial fluid culture has a sensitivity of 86 to 92% and specificity of 82% to 97% [22], and is recommended to inoculate in blood culture vials.

Microbiology plays an important role to identify the causing microorganism and to choose the best antimicrobial option. It is recommended to perform 3 to 5 biopsies from different sites around the prostheses [7]. The suggested culture media may include media for aerobic and anaerobic bacteria, and it is also recommended to inoculate in enrichment media such as blood culture bottles or thioglycolate broth [23, 24]. The number of days proposed to keep each sample is up to 14 days in order to recover different microorganisms such as those that have slower growth, such as *Propionibacterium acnes* [25•]. Alpha-defensin is a promising immunoassay that is not affected by systemic inflammation or antimicrobial therapy [26, 27].

Sonication of prosthetic material

This technique helps to dislodge biofilm and subsequently allows bacteria to grow in conventional culture media [28]. The diagnostic yield is higher than periprosthetic cultures in terms of sensitivity, being up to 88% [29–33]. It is preferred to use a solid container than a plastic bag to transport the pieces to the laboratory because it increases specificity [3••]. Briefly, the procedure is done with the following technique: Hartman solution is added to the container and then vortexed for 1 min, then the container with the prosthetic material is sonicated for 5 min + −5 kHz, then it is again vortexed for 1 min, and an optional centrifuged last step for 5 min. The fluid is finally plated onto solid agar [34]. The threshold for the procedure including the centrifugation step is 200 CFU per ml [35], and without it is 10 CFU per ml [33, 34]. Vortexing of prosthetic material is an option for those hospitals that do not have sonication equipment. This technique may help when synovial fluid or tissue cultures do not have enough yields or when antimicrobials were given within the 2 weeks before surgery [8].

Molecular studies

As in other infectious diseases, molecular diagnosis may help increase sensitivity and reduce the time compared to standard cultures. 16S rRNA PCR method is a broad range assay that may identify nucleic acid sequences conserved from bacteria [3••, 36]; however, these kind of studies give potential bias because of false-positive results limiting their interpretation in some cases [37]. They may be beneficial when the same amounts of samples as standard cultures are processed to increase sensitivity and specificity or when the patient has received antimicrobials in the previous 7 days [24]. Molecular studies in sonicated fluid are even more problematic to interpret if they are the unique positive result. Regarding multiplex 16S rRNA PCR assay to diagnose PJI, Borde et al. showed that this technique was not superior to conventional cultures in tissue samples [38•].

Imaging

Plain radiographs aid to suspect infection, as it can be seen component's loosening, soft tissue gas, lucency, or effusion; however, they are neither sensitive nor specific [3••]. Computed tomography and magnetic resonance may have artifact limitation, despite of using specialized software to decrease it presence [19••]. Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) has been used with a high yield excluding infection, albeit this technique has a high cost and is not available in most of the lower income countries [39, 40•]. Nuclear imaging studies are not recommended as follow-up studies due to false positivity for years.

Treatment

General aspects

Curing since the first treatment attempt is crucial because with each treatment failure, tissue damage and functional integrity are worse, and choosing the least invasive treatment that cures infection is the most rational approach. As data from controlled trials comparing different surgical procedures are lacking, treatment concepts vary between different centers, and recommendations are based on case series, expert opinions, and published guidelines [8, 16•]. Considering the prerequisites for the successful use of each surgical procedure, all surgical interventions have a favorable outcome in more than 80% of the patients [41, 42].

Surgical interventions

Antimicrobial treatment without any surgical intervention is not curative but only suppressive. There are four different curative options: DAIR, one-stage exchange, two-stage exchange, and removal without replacement. One- or two-stage exchanges have been associated with cure rates of greater than 80% [14]. In addition, in special situations, arthrodesis or amputation may be necessary [8]. Table 2 shows a brief summary of recommended surgical options according to clinical and microbiology presentation.

Debridement, antibiotics and implant retention (DAIR)

This is a potential surgical management option in two situations: early postoperative or late hematogenous PJI; however, the success rate is not inferior than one-stage exchange surgery (>80% cure rate), if the following conditions are fulfilled: (a) acute infection (duration of infectious symptoms: <3 weeks or <1 month after implantation), where bacterial biofilm is not yet fully established [14]; (b) stable implant (well-fixed); (c) pathogen susceptible to a biofilm-active antimicrobial agent; and (d) no sinus tract and no periprosthetic abscess. All other patients should proceed to one- or two-stage revision surgery. Open arthrotomy rather than arthroscopy is necessary for rapid and meticulous debridement of necrotic tissue [14]. In prosthetic knee infection, the reported success rate is better after arthrotomy than after arthroscopic debridement (86 versus 56%, showing >fourfold increase in the risk of treatment failure with arthroscopic debridement [3••]). In case of open

debridement, modular components are highly recommended to exchange; although there is little evidence [43–46], this maneuver reduces the failure risk by 33% [13••]. Patients who failed a DAIR procedure typically undergo a two-stage arthroplasty exchange. Measures such as intra-articular local antimicrobials placement or resorbable antimicrobial-impregnated pellets are not recommended because of lack of evidence [47–50].

One-stage exchange

This treatment option includes removal and reimplantation of the device during the same surgical procedure. It can be chosen for patients with prostheses hip infection [3••], good soft tissue envelope, and a pathogen that is susceptible to oral antimicrobial agents with excellent bioavailability and activity on biofilms [41]. However, it is crucial to identify the causative pathogen before the surgical procedure. In contrast to implant retention, stability of the implant is not required [8]. Generally, effective antimicrobial impregnated to bone cement is used [13••]. This procedure offers results comparable to those of a two-stage arthroplasty, although some series report higher rates of reinfection. Albeit it may cost up to 1.7 times less than a two-stage revision there have been no randomized trials comparing these approaches [13••].

Two-stage exchange

A staged exchange is the most common and decisive strategy in terms of infection eradication, with success rates of 87 to 100% in hip arthroplasty, and 72 to 95% in knee arthroplasty [3••]. It starts with thorough removal of all necrotic tissue, and the implant material before reimplantation of a new device that is performed at a second intervention. After removal of all foreign material, an antimicrobial-impregnated spacer, typically polymethylmethacrylate (PMMA), is inserted to get stability, allowing some degree of mobility, to prevent shrinking joint and to have a high local concentration of antimicrobials; however, the need of local antimicrobials in the spacer has never been proven in a comparative and prospective PJI trial. In between the two surgical procedures, the patient receives directed antimicrobial therapy to suppress infection. Reimplantation is delayed for at least 2 weeks of free-antimicrobial period in order to get reliable samples for microbiology [51, 52]. If there is evidence of ongoing infection, a repeat debridement procedure may be performed, followed by further antimicrobial therapy before reimplantation [3••]. As it is noticed, the main disadvantage is the need for two surgical interventions, prolonged disability, and the interval with the biomechanically suboptimal spacer [41].

Risk factors for treatment failure could be associated with important local changes, lymphedema with knee arthroplasty infection, the presence of a sinus tract, previous revision surgery, systemic diseases, negative culturing or drug resistant bacteria [50, 52, 53].

In the case of atypical bacteria or fungal infection this procedure is the best option; however, it is not as successful as treatment of common bacteria [13••].

Table 2. Surgical interventions suggested options according to clinical and microbiology presentation. [2, 3••, 7]

	DAIR	One-stage exchange	Two-stage exchange	Resection arthroplasty	Arthrodesis	Amputation
<1 month after surgery or <1 week of symptoms	✓					
>1 month after surgery or >3 weeks of symptoms		✓	✓			
Stable prostheses	✓					
Less virulent microorganism	✓	✓				
Multidrug resistant/ atypical/fungal infection			✓	✓	✓	✓
Presence of fistula			✓			
Good quality of soft tissues	✓	✓	✓			
Poor quality of bone stock				✓	✓	✓
Inability to tolerate revision arthroplasty				✓	✓	✓
Peripheral vascular disease or neurovascular injury						✓

**DAIR* debridment, antibiotic and implant retention

Other surgical procedures

There are some surgical procedures such as resection arthroplasty, arthrodesis, or amputation that are reserved for those non-candidate patients for the above strategies. When one- or two-stage exchanges are not suitable due to massive bone or soft tissue loss, highly resistant microorganisms, unacceptable medical or surgical risks from another reconstructive attempt or patient preference, resection arthroplasty without reimplantation is advised. This salvage strategy is reserved to avoid amputation after prior failed treatment attempts or for patients who are not candidates for DAIR or one-stage exchange and cannot or do not want to undergo multiple surgeries [3••]. In the case of hip resection, Girdlestone procedure, which includes removing of the femoral's head allowing it to fuse with acetabulum, results in a high rate of infection control [53, 54] and pain relief [55]; however, patients are typically left with significant limb length discrepancies, needing assistive devices for ambulation [3••]. Arthrodesis may be

performed in patients following resection of a knee arthroplasty; this procedure may provide additional mechanical support to allow ambulation. The IDSA (Infectious Diseases Society of America) and International Consensus guidelines recommend that amputation is considered a last resort when there are drawbacks to perform the previous options [2].

Antimicrobial treatment

Antimicrobial treatment always goes hand in hand with surgical treatment and remains only as a unique option for those patients who have contraindication to surgery or who do not wish to receive it. The antimicrobial recommendations are according to the decided surgical strategy and the microorganism isolated. In order to have the best microbiological information, and if the patient's clinical condition allows it, antimicrobial treatment must wait until samples are taken.

According to surgical strategy

When DAIR procedure is performed, antimicrobials are first administered for 2 to 6 weeks intravenously, then followed for a period of 3–6 months for total hip arthroplasty (THA) and 6 month for total knee arthroplasty (TKA) [56, 57]; however, some studies have not identified outcome differences from shorter periods of antimicrobial treatment, independently of the microorganism in cases of DAIR strategy, such as only 2 to 6 weeks [58–60]. When there is no microbiology information before the surgical procedure in early-onset infections, broad-spectrum antimicrobial are initiated and then adjusted according to cultures. Regarding the antimicrobial route administration for treatment initiation, either intravenous versus oral, there is scarce information suggesting that oral route has no outcome disadvantage, independently of the surgical approach [59]. A randomized control trial exploring the outcome between both administration routes of antimicrobials for PJI is in process [61•].

In those cases in which a one-stage exchange arthroplasty is accomplished, the management is similar to DAIR strategy [6]; although there is no consensus in antimicrobial duration, at least 2 to 6 weeks of treatment are suggested [8]. Antibiofilm therapy is given in DAIR and one-stage exchange procedures, as the device will remain in place [3••].

When two-stage exchange is performed, the intravenous antimicrobials duration is for 6–12 weeks; however, Silvestre et al. showed high success rates in revision knee prostheses when oral antimicrobial therapy was given for 5 weeks with only one previous intravenous week [62]. As in one-stage exchange the period of time is debatable, the consensus also suggested a period of 2 to 6 weeks [8]. An antimicrobial free period for 2 to 4 weeks is performed in practice in order to evaluate clinical stability, although there is no conclusive evidence supporting it.

Suppression therapy is reserved for those cases where it is not possible to perform a surgery, because patient's clinical condition or patient's preferences, where there is scarce bone stock or a high probability of progressive material loosening [2, 63, 64]. The antimicrobial choice must be patient-tailored, best-tolerated, and least toxic over the microbiota to avoid possible complications, such as *Clostridium difficile* infection.

According to isolated microorganism

Staphylococcus aureus (SA) infection is one of the leading microorganisms causing PJI. Favorable outcome with methicillin susceptible (MSSA) bacteria are more frequent than resistant (MRSA) [65]. For MSSA penicillin active against SA or first generation cephalosporins are the first treatment option rather than vancomycin, because of its better pharmacological properties in terms of bactericidal eradication. Recommended options for oral treatment are trimethoprim-sulfamethoxazole, quinolones, minocycline, doxicycline, or antistaphylococcal penicillins. In MRSA infection vancomycin is the first option; however, daptomycin and linezolid are good alternatives [2]. Coagulase-negative Staphylococci infections behaves similar to SA infection, so the recommendations are as for the former bacteria [43, 66].

When antibiofilm treatment is added, such as rifampin, from the beginning of treatment, the success rate is higher [67]. Intravenous antimicrobials should be administered for 4–6 weeks in cases where rifampin cannot be given. The same time of intravenous treatment recommendation is preferred for those infections different to Staphylococci genre, such as Gram-negative bacilli [3••]. Enterococcal infections susceptible to penicillin are ideally treated with either penicillin or ampicillin. In those ampicillin resistant bacteria or allergic patients, the best option is vancomycin or linezolid [2].

There is paucity information regarding Gram-negative PJI infection treatment and overall outcome. Depending on the type of Gram-negative bacilli (GNB) and its susceptibility, it is suggested the best pharmacological option; however, quinolones are the best choice for susceptible GNB. Rodríguez-Pardo et al. reported success rate of 79% in a study of only GNB PJI with DAIR treatment procedure [68•], and Zmistowski et al. reported success rates of 70% DAIR and nearly 50% with two-stage exchange procedure [69]. Combination therapy in *Pseudomonas aeruginosa* infection might be an option, however, there is scarce information [68•].

The epidemic of multidrug resistance (MDR) microorganisms has impacted the management of infectious diseases worldwide, for instance, a 19% resistance to ciprofloxacin and 11% of extended spectrum beta-lactamase (ESBL) in GNB were reported for PJI in Spain [68•]. Some options against MDR microorganisms are fusidic acid [70], linezolid [71], tigecycline [72], carbapenems [73], and colistin [74] with variable success rates.

Fungal infection is a less frequent complication, even though this infection represents a greater challenge. *Candida spp*. is the leading microorganism causing PJI; however, other fungi such as *Aspergillus spp*., and *Pseudollescheria spp*. have been reported [75–77]. The recommended antifungal drugs are fluconazole, echinocandin, and lipid formulation amphotericin B depending on the fungal susceptibility tests. Recently, there is an increasing amount of fluconazol-resistant *Candida spp*., which has limited its use as first line treatment. It is advisable to give antifungal treatments for 6 to 12 months [78].

Local antimicrobial therapy in PMMA cement

High local concentration of antimicrobial may achieve with PMMA cement spacers, increasing success rate probability [2, 79]. Cement spacers loaded with vancomycin, gentamicine, and tobramycine are mainly used in practice; however, there are different reports with other antimicrobials used. Therefore, the type and dose of elected antimicrobial should be individualized according to

the microbial susceptibility and patient's renal function because of the renal toxicity concern [8, 80–84].

Conclusions

The increasing number of joint arthroplasties around the world may lead a raise in PJI. This infection is a challenge for the collaborative group in terms of diagnosis and treatment. When the patient condition is identified objectively according to their evolution, technical possibilities, and microbiology, it is possible to get high treatment success rates. Although there is no universal diagnostic gold standard test to confirm PJI diagnosis, the use of specific criteria has clarified the identification of patients. Material sonication and molecular testing may help in cases where there is no microbiological recovery by conventional cultures. Combined surgical and antimicrobial treatment is essential, except in patients who decide to continue suppressive treatment. The DAIR strategy is the most indicated in early-onset infections. So far, there is no outcome difference between one- and two-stage exchanges. Antimicrobial treatment should be chosen according to the isolated microorganism, the patient's characteristics, and their pharmacological properties. Drugs with antibiofilm activity are highly recommended in Staphylococci PJI. Both the total time of antimicrobial treatment as well as the duration of the intravenous route is controversial; however, it appears that shortened treatments have same success rates as conventional ones.

Compliance with Ethical Standards

Conflict of interest

Dr. Franco-Cendejas reports personal fees from Pfizer and personal fees from Stendhal Pharma, outside the submitted work. Dr. Mondragón-Eguiluz reports personal fees from Pfizer, personal fees from Stendhal Pharma, personal fees from Eli Lilly, and personal fees from Astra-Zeneca, outside the submitted work. Dr. Vanegas-Rodríguez declares that he has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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