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Diagnosis, management, and prevention of prosthetic joint infections

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1. ABSTRACT

As the number of joint prosthesis replacements worldwide increases exponentially, prosthetic joint infection (PJI), associated with prosthetic implants, has become a devastating complication associated with high morbidity and substantial cost. Patients who develop PJIs typically require extended hospitalization, additional surgical procedures, and long courses of parenteral antimicrobials. Defining the diagnostic criteria is complicated by patient heterogeneity. No single routinely used clinical test has been shown to achieve the ideal sensitivity, specificity, and accuracy for the diagnosis of PJI. Goals of treatment are to eradicate infection, prevent recurrence, and preserve mechanical joint function. Meanwhile, preventive strategies should be used in a timely and appropriate fashion. The present review will discuss the diagnosis, management, and prevention of PJI.

2. INTRODUCTION

The development of modern total hip and knee arthroplasty represented a milestone in orthopedic surgery. Since then, there has been a dramatic increase in the number of joint prosthesis replacements performed. However, prosthetic joint infection (PJI), associated with prosthetic implants after total joint arthroplasty (TJA), is the most devastating complication and is associated with high morbidity and substantial morbidity (1, 2). The presence of a foreign body confers increased susceptibility to infection (3), with an incidence of 1.5-2.5% in total hip arthroplasty (THA) and total knee arthroplasty (TKA) before primary intervention. Higher rates (2-20%) have been reported after revision procedures (1). However, infection may ensue despite the use of perioperative antimicrobial prophylaxis and surgery, and, moreover, may

occur via hematogenous spread during the lifetime of the implant (4).

3. PATHOGENESIS

A common definition for PJI has not been established, although there are widely accepted diagnostic criteria (5, 6), as PJIs are generally classified into 3 phases according to the time of onset after surgery. Early-onset infection is defined as the appearance of signs and symptoms of infection within 3 months after arthroplasty; delayed-onset infection within 3–24 months; and late-onset infection as greater than 24 months. Interestingly, the distribution of patients in each category is approximately equal (7, 8). PJIs occur more frequently in patients with a previous revision arthroplasty and in subjects with diabetes mellitus, rheumatoid arthritis, obesity, neoplasm, and immunosuppression (9, 10). Surgical factors such as sterility, long operative times, and the use of antibiotic-impregnated cement also increase the risk of infection (11-13).

4. MICROBIOLOGY

Microorganisms may reach the prosthesis at the time of implantation or afterwards by hematogenous spread (9, 14). The development of biofilm has a strategic role in the pathogenesis of PJI, as microorganisms will adhere to the implant and form a biofilm, which affords protection from the host immune system and most antibiotics (7).

Almost any microorganism can cause PJI, but staphylococci (coagulase-negative staphylococci and *Staphylococcus aureus*) are the principal causative agents, accounting for greater than 50% of all infections after THA and TKA (7, 15). Polymicrobial infection is reported in 10–20% of PJIs, in which the most frequently identified organisms are methicillin-resistant *S. aureus* (MRSA) and anaerobes (16). The anaerobe *Propionibacterium acnes* accounts for an additional 10% of infections and is a common cause of PJI following shoulder arthroplasty (15).

5. CLINICAL PRESENTATION

5.1. Diagnosis

The presentation of PJI varies, ranging from a chronic indolent course characterized only by progressive joint pain, to fulminant septic arthritis. However, the diagnosis is not always clear because there are many noninfectious causes of prosthesis failure. Although a simple gold standard to confirm PJI is currently lacking, diagnostic criteria have been proposed. The presence of 1 or more of the following criteria is believed to be adequate for the diagnosis of PJI: acute inflammation on histopathologic examination of periprosthetic tissue; sinus tract communication with the prosthesis; gross purulence in the joint space; and growth of the same microorganism in 2 or more cultures of joint aspirates or periprosthetic tissue (15).

5.1.1. Aspiration of joint synovial fluid

In the absence of obvious signs and symptoms upon physical examination, further studies are required. Aspiration of joint synovial fluid using established criteria is typically the most valuable test for the diagnosis of PJI (15). A synovial fluid leukocyte count of greater than 1700 cells/mL, or differential with greater than 65% polymorphonuclear leukocytes is diagnostic of prosthetic knee infection in patients without inflammatory joint disease (17). In a study of 201 painful hip arthroplasties, other investigators have found that a synovial fluid leukocyte count of greater than 4200/mL was 84% sensitive and 93% specific, and that a leukocyte differential of 80% neutrophils was 84% sensitive and 82% specific for PJI (18).

5.1.2. Laboratory markers

Laboratory markers, such as leukocyte count, leukocyte differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are often closely related with PJI, but they are neither specific nor sensitive and may be elevated because of other inflammatory conditions (or, conversely, may be falsely negative in the context of suppressive antimicrobial therapy or low-virulence organisms) (15, 18). Thus, serial postoperative measurements are more informative than a single value. However, a normal ESR along with a normal CRP level is suggestive of a very low probability of infection (11). The roles of other novel markers, including interleukin-1 and -6 (IL-1), IL-6, procalcitonin, and tumor necrosis factor-alpha (TNF-α) remain to be clarified. (19-21),

5.1.3. Imaging studies

Imaging has an adjunctive role in PJI diagnosis, although most modalities have poor sensitivity and specificity. Plain radiographs are neither sensitive nor specific, but may be helpful in monitoring serial changes over time after implantation. Loosening of the prosthesis or bone loss around a previously well-fixed implant is associated with chronic prosthetic joint infection (22, 23). Computed tomography (CT) and magnetic resonance imaging (MRI) provide better differentiation between normal and abnormal tissues than plain radiography, and are useful in complex cases. However, they are limited by tissue artifact related to the metal implant, and MRI is limited to patients with MRI-compatible implants (24). On the other hand, radionuclide imaging is not affected by metallic hardware and is the imaging modality of choice for evaluation of suspected PJI (25). Positron emission tomography with fludeoxyglucose F18 has been studied as a possible diagnostic modality, although its clinical utility remains undefined (26-28).

5.1.4. Culture studies

Intraoperative periprosthetic tissue cultures are important to establish the presence of PJI and direct subsequent antimicrobial therapy when the diagnosis cannot be made preoperatively. Commensal organisms on the skin most commonly infect implantable biomedical devices (29). Usually, antimicrobials should be stopped several days before revision arthroplasty, because antimicrobial therapy results in the reduction of yield from both synovial fluid and operative cultures (7). The sensitivity of tissue culture increases as the number of specimens collected increases. Therefore, to accurately

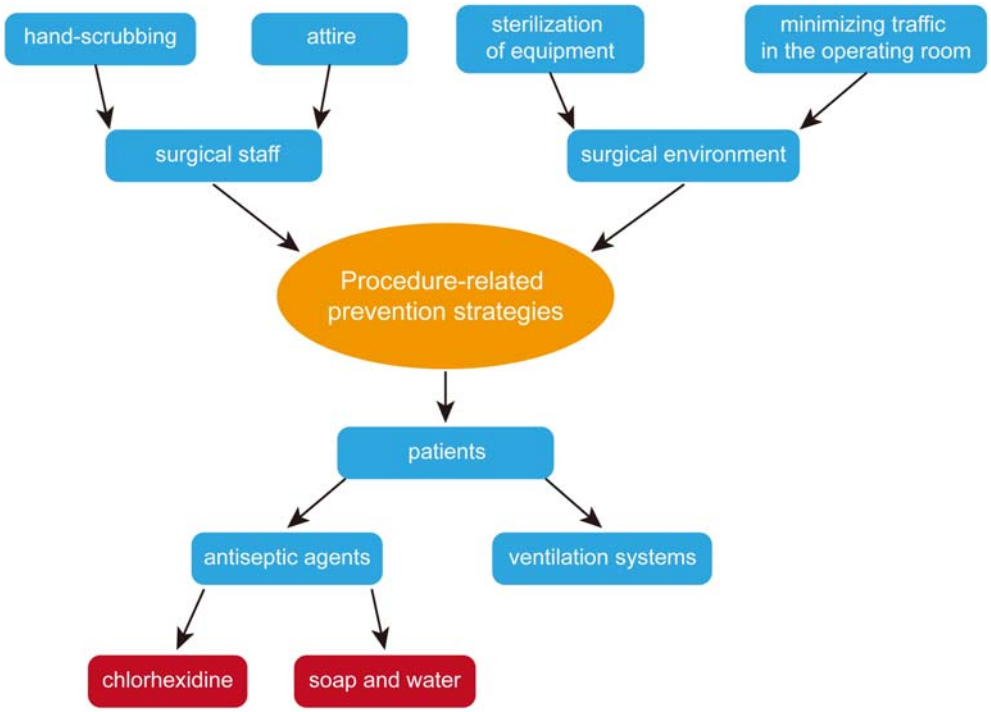

Figure 1. Procedure-related prevention strategies to reduce the microbial inoculum and prevent contamination of the surgical site. Important strategies include preparation of the surgical site with an hand-scrubbing and use of appropriate attire by the surgical staff, appropriate antiseptic agents and the use of appropriate ventilation systems by patients, and sterilization of equipment and minimizing traffic in the operating room. The antiseptic agents include chlorhexidine and soap and water. However, preoperative bathing with antiseptic agents is not recommended for prevention of TJA.

predict PJI, most experts recommend that sampling of 3 or more independent intraoperative tissue specimens (29-32).

5.2. Management

Management of PJI in arthroplasty poses the triple challenge of eradicating infection, preventing recurrence, and preserving mechanical joint function. Major decisions in PJI management are whether the implant should be retained, what surgical strategy should be used, and which antimicrobial treatment should be instituted. Optimal management achieves significantly better long-term outcomes (33, 34).

5.2.1. Medical therapy

Antimicrobial therapy is essential in the management of PJI, although there are no set standards and controversies exist regarding the ideal regimen and duration of administration (35). Antibiotics should be bactericidal against surface-adhering, slow-growing microorganisms in biofilm and should achieve high concentrations in the bone.

Rifampicin is highly effective against stationary phase staphylococci in clinical trials of PJI and is well absorbed orally (36, 37). It is generally recommended for use for the treatment of PJIs in combination with quinolones, in order to avoid the development of resistance. Its efficacy has been demonstrated in several studies (36, 38). Berdal *et al.* (38) observed that surgical debridement plus the combination of rifampicin/ciprofloxacin was successful in 83% of cases. A meta-analysis on the clinical efficacy of antibiotics for bone and joint infections showed a trend towards improved, long-lasting infection control with a rifampicin/ciprofloxacin combination versus ciprofloxacin alone in the treatment of orthopedic device related staphylococcal infections (absolute risk difference 28.9%) (39). In a recent prospective cohort study of *Staphylococcus*-infected orthopedic implants treated with long-term oral rifampicin/levofloxacin, Barberan *et al.* (40) reported a global failure rate of 35% (range 16.6–69.2%, $p<0.05$; higher for the knee) in patients with symptoms lasting from less than 1 to greater than 6 months (40). Alternative antimicrobial agents such as fusidic acid, trimethoprim/sulfamethoxazole, and minocycline can also be combined with rifampicin (41-43), whereas intravenous glycopeptides are primarily used treat PJIs caused by methicillin-resistant gram-positive bacteria (44). In patients with MRSA acquired postoperatively, continuous outpatient vancomycin infusion to acquire a steady-state over several months has been successful (45).

Newer antibiotics such as linezolid, daptomycin, and tigecycline have been introduced, although not fully approved, for PJIs. Linezolid is a bacteriostatic antibiotic that is also available in oral form and has excellent bioavailability. Taking advantage of the pharmacokinetic

profile, linezolid is a suitable alternative for the treatment of infections that require a prolonged treatment (46, 47). A retrospective study reported a greater than 80% success rate in PJIs treated with linezolid (48). Daptomycin has activity against most gram-positive bacteria, including MRSA and those with multidrug resistance, and is also able to kill stationary phase bacteria in biofilm present on implants (49). Falagas *et al.* (50) demonstrated its use in 20 patients with PJI and reported a cumulative cure rate of 81%. The optimal dose of daptomycin for PJI is still under evaluation, although a trial of daptomycin at the dose of 6 or 8 mg/kg/day is ongoing, with published data showing a higher failure rate in patients receiving 4 mg/kg/day or less (51, 52). Tigecycline is a novel broad-spectrum glycylcycline antibiotic, which has effective *in vitro* bacteriostatic activity against a broad range of gram-positive and -negative, atypical, anaerobic, and antibiotic-resistant bacteria, although there is a lack of data in the setting of PJI (53). In an experimental osteomyelitis model, the role of tigecycline was reportedly successful in 100% of orthopedic infections (52). However, human trials on the use of tigecycline in bone and joint infection are lacking.

5.2.2. Surgical therapy

The ultimate goal of PJI treatment is to restore a patient to a functional and pain-free joint status, which requires a combination of medical and surgical therapies. Although the use of antimicrobials alone to treat PJIs is usually inadequate, patient preference and the potential morbidity of further surgical intervention must be carefully considered. For patients who need additional surgery, there are several possible approaches, including debridement with retention of device (DRD), one or two stage exchange arthroplasty with re-implantation, arthrodesis (knee), and excision arthroplasty (shoulder, hip) (54-57). For patients with early-onset infection or acute onset hematogenously acquired infection, DRD followed by a prolonged course of antimicrobial therapy may be the most conservative and potentially successful option (15). DRD is appropriate for patients with intact overlying soft tissue or with a short duration of symptoms (fewer than 3 weeks), while not appropriate for those with unstable prostheses, sinus tract or abscess formation, or infections associated with multidrug-resistant organisms (58-62).

For most patients with delayed-onset infection, the preferred approach is staged replacement of the entire device, either as a single-stage exchange (SSE – including the excision of all prosthetic components and infected tissue and reimplantation of new components in the same operation – mainly for hip prostheses) or a two-stage exchange (TSE) for other prosthetic joints (knee, shoulder, or elbow) (15, 63). SSE is appropriate for patients with prolonged symptoms but with intact soft tissue and fewer virulent organisms, as it allows earlier mobility, but the risk of infection recurrence is greater (failure rate 0–14%) (64-66). In TSE, the prosthesis is removed and replaced temporarily with an antibiotic-impregnated polymethyl methacrylate spacer. After 2–8 weeks, the patient is reimplanted with a new prosthesis. Furthermore, extended courses of antimicrobials are still necessary. Although the cost is high, this procedure has the highest success rate, usually exceeding 90% (67, 68).

Surgical therapy is often followed by antimicrobial treatment. Although there is no standard dosage of optimal antimicrobial agents, 6 weeks of high-dose therapy after surgery is widely used. In all cases, clinicians select antimicrobial agents considering issues such as tissue penetration, tolerability, and bactericidal activity. Some clinicians favor follow-up courses of long-term oral therapy as suppressive or consolidation therapy if the device is retained, but the use of long-term oral antimicrobials remains controversial with the ideal length of suppressive therapy still unclear (61, 69). Some receive lifelong antimicrobials, whereas others have a defined length of therapy for 3 months for THA infection, and 6 months for TKA infection (5, 36, 70). Therefore, many factors should be considered regarding the choice of suppressive agents and length of therapy, such as clinician and patient preference, treatment failure, and adverse drug events.

5.3. Prevention

The principles for PJI prevention are the same as that of other types of surgical site infections and are generally classified into 3 categories: procedure-related issues, patient-related issues, and perioperative antimicrobial prophylaxis.

5.3.1. Procedure- and patient-related issues

Procedure-related prevention strategies aim to reduce the microbial inoculum and prevent contamination of the surgical site by surgical staff, instruments, and the environment. Important strategies include preparation of the surgical site with appropriate antiseptics, hand-scrubbing and appropriate attire by the surgical staff, sterilization of equipment, minimizing traffic in the operating room, and the use of appropriate ventilation systems (71). Recently, antisepstic skin preparation has attracted attention. Two clinical studies on preoperative skin preparation in abdominal surgery patients demonstrated that iodine-containing products effectively prevented surgical site infections, although a comparison had not been performed specifically in the setting of TJA (72, 73). Zywiel *et al.* (74) recently reported that patients who underwent skin cleansing (preoperative bathing) with chlorhexidine-impregnated cloths prior to TKA had a lower rate of surgical site infection. However, a conflicting study performed by Webster *et al.* (75) demonstrated that preoperative use of chlorhexidine-containing products conferred no advantage over bathing with soap and water. Therefore, preoperative bathing with antiseptic agents is not recommended for prevention of TJA. Besides, there are numerous effective prevention strategies that address modifiable patient-related factors, such as strict perioperative blood glucose control for diabetics and minimal use of immunosuppressive medications.

5.3.2. Perioperative antimicrobial prophylaxis

Appropriate use of perioperative systemic antimicrobial prophylaxis is important to reduce the chance of introduction of microbial inoculum into the surgical site.

Essentially, meticulous surgical technique is essential to reduce infection after joint arthroplasty. Efforts should be made to minimize the duration of surgery, because longer operative time likely results in higher rates of infection (76). Double gloving and an outer cloth glove are recommended as they have been shown to effectively reduce infection after joint arthroplasty (77). Gore-Tex gowns may also prevent bacteria transmission up to 1000-fold more effectively than cotton gowns (78). In addition, frequent exchange of suction tips, saline irrigation, and gentle tissue handling all contribute to a significant reduction in wound bacterial counts (79, 80). However, more studies are required before routine implementation of these techniques.

The choice of antimicrobial agents for perioperative prophylaxis is another important issue, as most clinicians choose agents based on the most likely pathogens to cause surgical site infections. *Staphylococci*, which are typically present on the patient's skin at the time of surgery, are the most common pathogens in PJIs. Hill et al. (81) reported that antimicrobial prophylaxis with cefazolin, a first-generation cephalosporin, significantly reduced the risk of PJI. This agent has activity against gram-positive bacteria (methicillin-susceptible staphylococci, streptococci) and some gram-negative bacteria (Escherichia coli and Klebsiella), while it has no effect against enterococci and is hence recommended as the first-line agent for antimicrobial prophylaxis in TJA (82). Alternatively, as a second-generation cephalosporin, cefuroxime has activity against staphylococci and streptococci as well as some gram-negative bacteria, and may be used in THA prophylaxis while also equally efficacious in preventing PJI (82, 83). For patients with severe □eta-lactam or known cephalosporin allergies, cefazolin or cefuroxime should be strictly avoided and vancomycin or clindamycin used instead (82).

Importantly, the timing of administration of perioperative prophylactic antimicrobials should be addressed, to achieve adequate serum and tissue minimum inhibitory concentrations. For example, preoperative antibiotics should be given within 1 hour of incision to maximize tissue concentrations. Classen *et al.* (84) reported that patients who received prophylactic antimicrobials within 2 hours of incision were less likely to develop surgical site infections than those who received them earlier (>2 h preoperatively) or later (after incision) (84). Compared with early studies that demonstrated that antimicrobials often lasted for several days postoperatively, it is now recommended that prophylactic antimicrobials should be not be continued for longer than 24 hours postoperatively in most types of elective surgery (71). The explanation for this is that longer courses of postoperative antimicrobial prophylaxis are more likely to result in acquisition of antimicrobial-resistant microorganisms (85).

Adverse events associated with perioperative prophylactic antimicrobials are relatively uncommon because the duration of therapy is usually short. However, adverse drug events are one of the most common occurrences among hospitalized patients. Gray *et al.* (86) reported that antimicrobials accounted for only 10.7% of preventable adverse drug events, with diarrhea as predominant. However, while enteral symptoms are common side effects of most antimicrobial agents, a more serious complication is *Clostridium difficile* infection, especially in older patients. The choice of antimicrobials should be based on the duration of surgical prophylaxis, as the most frequently perioperative antibiotics used in TJA, cefazolin and cefuroxime, do not generally lead to adverse outcomes when given for a short duration. Prolonged courses of cephalosporin therapy, on the other hand, may result in leukopenia, thrombocytopenia, eosinophilia, and hepatotoxicity (87). Vancomycin and clindamycin, antibiotics used in patients with cephalosporin allergy, are also occasionally associated with adverse events (88).

6. CONCLUSION

PJIs are difficult to diagnose and treat, are associated with high morbidity and substantial cost, and thus represent an extraordinary challenge for clinicians. The diagnosis, management, and prevention of PJIs have not yet been resolved. The diagnosis of PJI often cannot be fully established until the prosthesis is removed, and management often requires both surgery and prolonged antimicrobial therapy. On the other hand, prevention of PJI requires a multifaceted approach. An important component of prevention is perioperative antimicrobial prophylaxis. Although TJA has been widely investigated, additional research is still required to determine the best approach for prevention of PJI.

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Abbreviations: CRP, C-reactive protein; DRD, retention of device; IL, interleukin; MRI, magnetic resonance imaging; PJI, prosthetic joint infection; SSE, single-stage exchange; THA, total hip arthroplasty; TJA, total joint arthroplasty; TKA, total knee arthroplasty; TNF, tumor necrosis factor; TSE, 2-stage exchange.

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