Prosthetic Joint Infections: an Update

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Abstract

Purpose of Review Prosthetic joint infection (PJI) is a rare but serious complication that is frequently misdiagnosed. We aimed to highlight the nuances of PJI diagnosis and antimicrobial therapies and provide clarity in key areas of management.

Recent Findings Current research in PJI centers on a potential role for diagnostic biomarkers, molecular techniques, and implant sonication to reduce culture-negativity rates. The optimal duration of antimicrobial therapy remains controversial.

Summary A high clinical index of suspicion for PJI combined with data from multiple preoperative and intraoperative tests enables timely diagnosis and treatment. Biomarkers, molecular methods, and implant sonication are currently adjunctive to traditional diagnostic techniques. Shorter courses of antimicrobial therapies as well as the role of chronic suppressive therapy need confirmation by randomized controlled trials. Existing practices for preoperative dental prophylaxis and treatment of asymptomatic bacteriuria warrant revision based on evidence arguing against risk for PJI.

Keywords Prosthetic joint infection · Diagnosis · Management · Controversies · Suppressive antibiotic therapy

Introduction

Joint replacement surgery is a life-enhancing procedure for millions of people each year. It is projected that by the year 2030, approximately four million total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) will be performed per year in the USA. While majority of individuals do considerably well after joint arthroplasty, a minority may experience prosthetic joint infection (PJI), a rare but devastating surgical complication. Preventive perioperative measures, such as antimicrobial prophylaxis, has reduced the rate of PJI to less than 2%, but the high number of joint implantations projects an infection rate of 12,000 implants per year [1].

PJI, also known as periprosthetic infection, is defined as infection involving the joint prosthesis and adjacent tissue. It is perhaps the most challenging complication associated with joint arthroplasty [2, 3] due to difficulties in diagnosis [4–6], unpredictability of occurrence [7, 8], and the frequent requirement for prolonged antimicrobial therapy and multiple surgical interventions [9, 10]. In this article, we will review its epidemiology and highlight recent advances in the diagnosis, management, and prevention of PJI.

Epidemiology

Incidence

The incidence of PJIs continues to be low but has increased over recent years. In the USA, the Nationwide Inpatient Sample (NIS) shows that the annual PJI incidence rate increased from 1.99 to 2.18% for hip arthroplasties and from 2.05 to 2.18% for knee arthroplasties between 2001 and 2009 [11]. Similarly, the Nordic Arthroplasty Register Association found an increase in the cumulative 5-year revision rate for infection in hip arthroplasties, rising from 0.46% during the period from 1995 to 1999 to 0.71% during 2005 to 2009 [12]. Primary shoulder arthroplasties showed similar infection rates.
ranging from 0.8 to 1.46% [13], and a systematic review of elbow arthroplasties found that 3.3% become infected [14].

**Economic Impact**

The estimated total hospital cost incurred for treating PJI cases in the US was $320 million in 2001 and $566 million in 2009 [11]. The total cost incurred with a PJI is highly variable and largely dependent on the treatment strategy utilized. For example, cost analysis of debridement and retention for management of PJI was 3.1 times more expensive than primary arthroplasty [15]. In contrast, the cost of PJI managed by two-stage exchange was 2.8 times and 4.8 times greater than aseptic revision and primary arthroplasty, respectively [3]. Notably, other direct and indirect expenses, such as time lost due to immobility, cost of prolonged rehabilitation, and cost of anti-infective therapy, are all unaccounted for, highlighting the fact that the financial burden incurred by PJI is grossly underestimated.

**Risk Factors**

Multiple studies have highlighted the many number of risk factors causing PJI that involve both the patient (intrinsic factors) and the environment (extrinsic factors) in the pre-, intra-, or postoperative periods [16].

**Intrinsic Factors**

Patient level risk factors may be modifiable or non-modifiable. Eighty percent of patients who are candidates for arthroplasty have modifiable risk factors. The most common are obesity (46%), anemia (29%), malnutrition (26%), and diabetes (20%) [17]. Optimization of these risk factors prior to surgery may help decrease the risk of postoperative infection.

Obesity, often defined as body mass index (BMI) of ≥35, has been associated with an increased risk of infection in most studies [18–20, 21•, 22–24]. A possible reason is the prolonged operative duration in obese patients; in one study, for example, each 1-kg/m² increase in BMI increased the operative time by about 1 min [25]. In contrast, BMI ≤ 25 was also associated with increased risk of PJI and is thought to reflect nutritional reserve, immunosuppression, and underlying rheumatoid arthritis [26•].

Often, it is difficult to separate the relative contribution of the underlying illness, the accompanying comorbid conditions, and the therapy used [27•]. Diabetes have a fourfold higher infection risk after arthroplasty, particularly if the diabetes is poorly controlled [28]. This underlying vulnerability to infection is not clearly understood but is likely multifactorial: it may be due to increased biofilm formation in the presence of hyperglycemia [29], dysfunctional leukocyte function, or microvascular changes in patients with longstanding diabetes that influence wound healing and the development of superficial surgical site infections [27••]. Regardless, patients with hyperglycemia alone or unrecognized diabetes seem to be at higher risk of postoperative complications.

The vulnerability to infection of patients with rheumatoid arthritis (RA) is likely twofold: due to the disease itself and disease modifying therapies. The postoperative infection rate likely increases if the disease is not controlled, becomes more chronic, or with the use of biologics [30]. Corticosteroids increase the infection risk in a dose-dependent manner. While low-dose prednisone (e.g., less than 10 mg/day) modestly increases the infection risk [31], a dose above 10 mg/day increases the risk by four- to sevenfold. Thus, it seems reasonable to wait for the effective corticosteroid dose to be as low as possible, preferably under 10 mg/day, or even 5 mg, before contemplating arthroplasty. Methotrexate does not increase the infection risk and need not be stopped preoperatively. Biologic disease-modifying antirheumatic drugs (DMARDs) that inhibit tumor necrosis factor alpha (TNF-α) or interleukin-6 (IL-6) increase the risk of surgical site infection after joint arthroplasty, but the limited number of patients studied preclude a conclusion about their impact on PJI [30, 32]. In general, it is recommended that these treatments be discontinued at least 2–6 weeks prior to arthroplasty, depending on the drug’s half-life [16].

Non-modifiable patient risk factors include gender, [8, 12, 18, 33, 34], age [35], genetic predisposition [36, 37], history of prior bacteremia in the previous year [38], and antecedent septic arthritis of the index joint [39•].

**Extrinsic Risk Factors**

Extrinsic risk factors include environmental or procedure-related factors. Several postoperative complications are associated with increased risk of PJI, including hematoma, superficial surgical site infection, wound drainage, and wound dehiscence [23, 24, 38, 39•, 40]. Prolonged operating time is associated with an increased risk of PJI [7, 8, 33, 39•, 41], with a 9% increase in risk for each additional 15-min increment [21•]. This may be due to an increased time available for microbial contamination of the joint or may be a surrogate for other comorbidities, such as obesity, or both [27•].

Perioperative infection at another site, including the urinary or respiratory tract, is also associated with an increased risk of PJI [22, 23, 40]. Secondary bacteremia with *Staphylococcus aureus*, in particular, increases risk [42•]. In contrast, a recent randomized study showed that asymptomatic bacteriuria does not increase the infection rate [43, 44•]. As a consequence, neither antibiotic treatment nor delay in surgery is indicated in cases of preoperative asymptomatic bacteriuria.

**Composite Risk Scores**

Composite risk scores are available and can be used to stratify the risk for PJI. In a large case control study, a
higher National Nosocomial Infections Surveillance (NNIS) System surgical score, which includes the length of the surgical procedure, the American Society of Anesthesiologists (ASA) preoperative assessment score, and surgical wound classification for each procedure, correlates with increased odds of infection [39•]. An elevated ASA score alone, estimating the burden of systemic disease, has also been associated with an increased risk of infection [20, 21•, 23, 40].

The Mayo Clinic PJI score, although not validated, uses a numerical score to predict PJI based on assessment at the time of joint arthroplasty implantation or 1 month later [26•]. It includes the BMI, history of surgery and arthroplasty, immunosuppression, ASA score, operative time, and the presence of postoperative wound discharge. In the near future, computerized evaluation or self-assessment tools for the infection risk may also be available [45].

**Clinical Presentation**

The clinical manifestations of PJI are highly variable and dependent on several factors: the virulence of the organism, the host immune response, the pathogenesis and timing of infection, and the joint involved. Signs or symptoms of PJI can be local or systemic.

In general, the Infectious Disease Society of America guidelines recommend that PJI should be suspected in patients with any of the following [46••]: a sinus tract or persistent wound drainage over a joint prosthesis, acute onset pain of a prosthesis, or any chronic painful prosthesis at any time after prosthesis implantation, particularly in the absence of a pain-free interval, in the first few years following implantation or if there is a history of prior wound healing problems or superficial or deep infection.

**Microbiology**

Gram-positive organisms account for the majority of arthroplasty infections, regardless of the timing of infection, or the type of arthroplasty. This is driven largely by *S. aureus* and coagulase-negative staphylococci, which contribute between 50 and 60% of PJs, while streptococci and enterococci together account for only approximately 10% of cases. Aerobic Gram-negative bacilli are rarely involved in PJs [47]. Culture negative PJI can occur, either because of prior antimicrobial use or fastidious organisms. A thorough discussion of the different organisms responsible for PJI is discussed elsewhere [47] and is beyond the scope of this review.

**Special Populations**

**Antibiotic Dental Prophylaxis**

The use of systemic antimicrobials for prophylaxis prior to dental procedures among patients with a prosthetic joint remains common practice despite evidence that refutes the tradition. In 2015, the American Dental Association Council on Scientific Affairs published a clinical practice guideline on the use of prophylactic antibiotics in patients with prosthetic joints undergoing dental procedures [48]. Among four studies [40, 49–51], three [40, 50, 51] showed no association between dental procedures and PJI, with odds ratios of 0.56–1.53. Based on these results, the panel recommends against routine use of prophylactic antibiotics prior to dental procedures for prevention of PJI. However, despite the evidence, there is reluctance from both patients and professionals to discontinue this common practice. The underlying reasons for this reluctance to change need to be addressed by future studies.

**PJI Among Immunocompromised Hosts—Transplant Recipients**

Despite the increasing number of organ transplantations, only two large studies [52, 53] have assessed the risk of PJI among transplant recipients. A large retrospective review from 1989 to 2009 [53] identified 12 solid organ transplant (SOT) recipients with PJI from a total of 367 recipients with a prosthesis implant. These occurred in eight renal, three liver, and one heart transplant recipient, respectively. The number of hip (6/12) and knee (6/12) arthroplasty infections was evenly distributed. The observed time to prosthesis failure ranged from 0.5 to 148 months after implantation. Gram-positive bacteria (staphylococci and streptococci) were the causative agent for most SOT recipients. Interestingly, there was no statistically significant association between traditional risk factors such as obesity or diabetes mellitus and PJI, although numbers were small. Most (10/12) patients had good outcome, with no recurrence of infection, although four of them were maintained on chronic suppressive therapy.

In contrast, in a large retrospective review of bone and joint infections among 5861 hematopoietic stem cell transplant (HSCT) recipients, only six were PJs—three hip, two knee, and one elbow. Median age was 61 years (range 45–69), and time to infection from date of transplant was 38 months (range 6–99). *Staphylococcus* sp. was the most common pathogen isolated in 5/6 cases. Half required two-step arthroplasty exchange. Majority (5/6) recovered from the infection and were symptom-free at time of last follow-up.

Although numbers currently appear to be small, the increasing number of arthroplasties performed in both SOT and HSCT recipients is anticipated to rise further, and more
studies are necessary to understand the nature of PJIs in these unique populations.

### Diagnosis

The diagnosis of PJI is often challenging because its definition is not standardized. Recognition of PJI can be delayed if the onset is late, or the only presenting symptom is pain at the site of implant. The most important differential is aseptic loosening of the joint, as treatments are radically different. Ultimately, accurate diagnosis of PJI rests on a combination of a high clinical index of suspicion, detailed history and physical examination, and analysis of synovial joint fluid, laboratory markers of inflammation, microbiological data, and intraoperative findings [46-••]. Over the past 6 years, the IDSA and Musculoskeletal Infection Society (MSIS) have each published diagnostic criteria for PJI in attempts to provide homogeneity to the interpretation of the available diagnostic modalities. With some minor differences, both sets of criteria incorporate pre- and intraoperative clinical features suggestive of PJI [46-••, 54] (see Table 1).

### Preoperative Diagnostic Tools for PJI (Fig. 1)

#### Laboratory Studies

The most commonly used screening tests to diagnose PJI are white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Based on previous publications, ESR > 30 mm/h and CRP > 10 mg/L are considered elevated [55]. However, none of these tests reliably predict the presence or absence of infection [56–58]. These markers may be normal in PJI and can be affected by postsurgical inflammation (for at least 2–4 weeks postop), inflammatory arthritis, intra-articular bleeding, as well as inter-laboratory variations, age, and patient medical comorbidities. CRP may be more accurate than ESR in predicting PJI [56, 57, 59]. However, combination of both markers may afford the best positive and negative predictive values [57, 59, 60].

In the febrile or septic patient with a painful prosthetic joint, blood cultures may help rule out concomitant bacteremia and should be sent prior to initiating antimicrobial therapy.

One of the most important diagnostic tools for PJI is synovial fluid analysis. Arthrocentesis should be undertaken in all patients with an acutely painful prosthesis, in patients with chronic or indolent symptoms, or those with an unexplained elevated ESR or CRP and a painful implant. Synovial fluid should be submitted for cell count and differential, crystal analysis, Gram stain, and aerobic and anaerobic cultures. Synovial fluid cell counts evolve over time after surgery [61], and the optimal threshold used to differentiate between septic and aseptic failure of the joint is debatable [62]. In general, studies show that the synovial fluid WBC count and %PMN is much higher in infected than uninfected joints, cut-off values for PJI are lower than those established for native joint septic arthritis and, synovial WBC is a high-quality diagnostic tool for PJI [57, 63–65].

In a prospective study of preoperative synovial fluid analysis from failed TKAs at 6 months or longer postimplantation, a synovial fluid leukocyte differential of > 65% neutrophils or a leukocyte count of > 1700 cells/μL had 97 and 94% sensitivity and specificities of 88 and 98%, respectively, to detect infection. None of these patients had underlying inflammatory joint disease [65]. A prospective study of patients with THA-associated infection showed a leukocyte count of 4200 cells/μL had a sensitivity of 84% and a specificity of 93% to detect PJI [66]. Recent studies further indicate that the synovial fluid WBC and %PMN cut-off values for early (< 6 weeks postop) TKA and THA infection are higher than those employed for chronic PJI [62, 67, 68]. Therefore, interpretation of synovial fluid results should take into account the time since prosthesis implantation, site of affected prosthesis (hip, knee) and recent antibiotic exposure.

Recently, there has been increasing interest in a potential role for pro-inflammatory serum and synovial fluid biomarkers to achieve rapid diagnosis of PJI [69]. Serum biomarkers of interest include IL-6, IL-4, and TNF-α, with multiple studies showing elevated IL-6 levels in PJI that return to normal more rapidly than CRP or ESR levels after surgery [56, 70, 71]. However, serum biomarkers are costly, lack sensitivity, and specificity for PJI and are not routinely measured at most laboratories. Alpha-defensin, a naturally occurring antimicrobial peptide released from activated neutrophils, is the only commercially available synovial biomarker for PJI. It has a reported sensitivity of 97% and specificity of 96–98% for the diagnosis of PJI. Importantly, it is unaffected by coexisting inflammatory conditions and prior antibiotic administration, although metallosis can cause false-positive results [72–73]. At present, cost, questionable specificity, and lack of long-term performance studies, including its ability to confirm resolution of infection between stages of a revision arthroplasty, preclude this biomarker’s widespread utilization.

#### Microbiologic Studies

Culture growth of the same microorganism from multiple specimens remains the cornerstone for the diagnosis of PJI. About 7–39% PJI cases are culture-negative [76]. Preoperative antimicrobial therapy may cause false-negative culture results in > 50% of cases [57, 76]. Other attributable factors are inability of traditional tissue cultures to recover fastidious or biofilm-associated bacterial pathogen, unusual microorganisms (e.g., fungi, mycobacteria), inappropriate culture media, or inadequate transport time. In order to maximize
Table 1 Definition of PJI by society statement

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<tr>
<td>1. Sinus tract communicating with the prosthesis; or</td>
<td>1. A sinus tract that communicates with the prosthesis</td>
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<td>2. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from</td>
<td>2. Two or more intraoperative cultures or combination of preoperative aspiration and intraoperative</td>
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<td>the affected prosthetic joint; or</td>
<td>cultures that yield the same organism (indistinguishable based on common laboratory tests including</td>
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<td>genus and species identification or common radiographs)</td>
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<td>3. Four of the following six criteria exist:</td>
<td>3. The presence of acute inflammation on histopathologic examination of periosteal tissue at the time of</td>
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<tr>
<td>a. Elevated serum erythrocyte sedimentation rate; serum C-reactive protein</td>
<td>surgical debridement or prosthesis removal as defined by the attending pathologist</td>
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<td>b. Elevated synovial leukocyte count</td>
<td>4. The presence of purulence without another known etiology surrounding the prosthesis</td>
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<td>c. Elevated synovial neutrophil percentage</td>
<td>Diagnosis made if any present</td>
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<tr>
<td>d. Isolation of a microorganism in one culture of periosteal tissue or fluid</td>
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<td>e. Purulence in the affected joint</td>
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<td>f. Greater than five neutrophils per high-power field in five high-power fields</td>
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<td>observed from histologic analysis of periosteal tissue at 9400 magnification</td>
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<td>Diagnosis made if one, two, or three present</td>
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Ref: Mayo Clinic infectious diseases subspecialties update May 7–9, 2015

culture yield, antibiotics should be withheld at least 2–4 weeks prior to obtaining synovial fluid or tissue samples, and multiple intraoperative specimens (minimum of 3) should be obtained for aerobic and anaerobic cultures. Microbiologic samples should include tissues from the joint capsule, synovial lining, curedt bone marrow, bone fragments, and any purulent or necrotic areas. Fungal and mycobacterial cultures should be submitted in cases of chronic, indolent or refractory infection, previously culture-negative cases, or immune-compromised patients. Swab cultures of sinus tracts or superficial wounds are strongly discouraged because of high discordance between swab and bone cultures [77]. Growth of skin bacteria from one of several intraoperative specimens, such as coagulase-negative staphylococcus, Propionibacterium acnes, or Corynebacterium spp., is typically considered contamination, unless the same are also retrieved from a preoperative sample.

Recently, PCR amplification of bacterial 16S rRNA gene and implant sonication to dislodge implant-associated bacterial biofilms have been gaining attention in efforts to circumvent the dilemma of culture-negative PJI [78–80]. PCR techniques are non-standardized for PJI assessment, the optimal clinical sample for PCR application is unknown, and published studies show mixed results for sensitivity and specificity for PJI diagnosis [81, 82, 83, 84, 85]. In cases of prior antibiotic exposure, the sensitivity of broad-spectrum PCR is higher than culture, at about 70% [83, 86]. In the original study on implant sonication, the sensitivity of a periosteal sonication-fluid culture for the diagnosis of hip and knee PJI was higher than that of a single periosteal tissue culture (78.5% vs. 60.8%, respectively) but became equivalent with collection of >3 tissue cultures. Implant sonicate-fluid culture was more sensitive than tissue culture in cases of antibiotic exposure in the 2 weeks prior to sampling (75% vs. 45%, P < 0.001). However, the sensitivities of implant sonication are inconsistent across studies. Sonication is also more time-consuming and labor-intensive than tissue culture. At this time, implant sonication and molecular diagnostics are recommended only as complementary tests.

Histopathology

Histopathological finding of at least 5 PMNs/hpf on frozen section of the periosteal tissue in at least 5 hpf has high sensitivity (> 80%) and specificity (> 90%) to confirm PJI [87, 88]. Inadequate sampling of infected areas and lack of expertise of the pathologist can hamper interpretation.

Radiological Studies

Radiological modalities, including X-ray, MRI, CT, and nuclear medicine studies, play a limited role in PJI diagnosis. X-ray is useful to screen for prosthesis loosening and fracture but lacks sensitivity and specificity to detect PJI. Use of MRI, CT, and FDG-PET is limited because of cost and image distortion from metal. Of the available nuclear medicine studies, combined labeled leukocyte and bone marrow imaging with 99mTc sulfur colloid has been reported to have >95% accuracy in diagnosing PJI and is useful because it is unaffected by metallic hardware [89, 90]; however, it is a costly test and not routinely available.

Treatment

The goal of PJI treatment is a functional and pain-free joint. Unfortunately, PJI eradication can be challenging due to the frequent need for multiple surgeries and extended antimicrobial courses. Microbial factors, primarily hardware-associated
biofilm production, not only render diagnosis difficult but also pose significant challenges for treatment. Biofilm-encased organisms are characteristically resistant to eradication by antimicrobial therapy alone, and infection relapse is common. Meticulous surgical debridement is critical to treatment success. A multidisciplinary approach, involving close collaboration between the patient, the orthopedic surgeons, infectious disease consultants, and medical physicians, allows for optimal treatment of PJI.

**Surgical Treatments**

The most common surgical treatments for PJI include debridement and retention of the prosthesis, one- or two-stage exchange, resection arthroplasty, arthrodesis, and amputation. There are no published randomized clinical trials to address optimal selection of these surgical procedures. Therefore, the orthopedist’s decision to undertake a particular surgical approach rests on patient preference and host and pathogen-
related factors. Based on published data, IDSA guidelines have incorporated treatment algorithms for PJI in various arthroplasties, which are shown in Figs. 2 and 3 [46**, 91].

In Europe, management of PJI is most often with a one-stage procedure or “direct exchange” [91], whereas the two-stage procedure is preferred in the USA [92].

One-stage exchange involves removal of all prosthesis components and cement, debridement of devitalized bone and tissue, and implantation of a new prosthesis in the same surgery. Although less morbid and costly than a two-stage arthroplasty, a positive outcome rests heavily on the condition of available bone stock and surrounding tissues, extent of debridement, virulence of the pathogen, and availability of appropriate antimicrobial therapy. Reported success rates of direct exchange for THA are 80–90% [46**].

For patients with a sinus tract to the prosthesis, devitalized soft tissue and inadequate bone stock, unstable prosthesis, prior revision arthroplasties or PJI or current infection with virulent pathogens, a two-stage exchange provides the best clinical outcome [46**, 92]. In the first stage, the procedure entails complete removal of hardware, meticulous debridement of infected tissue, and placement of an antibiotic-impregnated cement spacer, followed by a prolonged course of antimicrobial therapy. Between stages, wound healing and trends in ESR and CRP are used to guide clinical response. A 2–4-week antibiotic-free interval is typically recommended before the second stage in order to enhance yield of pre- or intraoperative cultures. This interval is especially relevant in management of infection from virulent organisms, such as *S. aureus*, enterococci, Gram-negative bacteria, multidrug-resistant organisms, and fungi. In the second stage, the decision of spacer exchange or prosthesis re-implantation relies on intraoperative tissue evaluation and results of pre- or intraoperative synovial fluid analysis and histopathology. A major disadvantage of the two-stage approach is the need for multiple surgeries and prolonged rehabilitation. Reported success rates are 80–90% [93].

Debridement and implant retention (DAIR) typically involves exchange of modular components and is frequently adopted for the elderly patient with comorbidities who is unable to undergo two-stage revision arthroplasty. Success rates
Fig. 3  Algorithm for the treatment of patients with infections not qualifying for implant retention. Adapted with permission from [91]

are variable. Important criteria determining success are a short duration of symptoms (< 3 weeks), early (<3-month postimplantation), acute, hematogenous PJI, absence of a sinus tract, and a stable prosthesis. Literature on DAIR can be difficult to interpret because of differences in patient selection, type of implanted devices, infection definition, follow-up periods, and selection and duration of antimicrobial therapies [46••, 91, 94]. Consistently identified factors for failure are duration of symptoms (>7 days), infection with virulent microorganisms, and presence of a sinus tract [95–99].

In cases of refractory or relapsing infection despite maximal medical and surgical efforts, treatment options include resection arthroplasty (permanent removal of implant) with or without arthrodesis and limb amputation.

Antimicrobial-impregnated static or articulating spacers are often used to manage dead space and deliver high doses of local antimicrobial therapy until placement of a permanent prosthesis. The antibiotic-impregnated cement is either premixed or mixed with one or more antimicrobial agents by the operating surgeon. There have been no randomized controlled trials to evaluate an independent benefit of this approach, and doses of impregnated antimicrobials are not standardized [100]. Typical antibiotic combinations are vancomycin and an aminoglycoside, or beta-lactams, daptomycin, and amphotericin. Of concern are the increasing reports of nephrotoxicity from systemic leaching of the drugs [100] and the use of spacers in PJI with MRSA, small-colony variants, and fungi, since such pathogens tend to persist as implant-associated biofilms. Published reports on the last issue show mixed outcomes [91, 101, 102].

**Antibiotic Therapy**

The principles of antibiotic therapy in PJI are dictated by the need to attain prolonged, therapeutic drug levels within bone tissue and antimicrobial activity against stationary-phase organisms (biofilm-encased organisms). For patients with either DAIR, direct exchange or two-stage exchange with a short interval, most experts propose a total treatment period of 3 months for hip prostheses and 6 months for knee prostheses [46••, 91]. The intravenous route of antibiotic administration is favored for the initial treatment phase, usually for 4–6 weeks followed by oral therapy. Resection arthroplasty is usually followed by intravenous antimicrobial or highly bioavailable oral antimicrobial therapy for 4–6 weeks only. In Europe, early transition from intravenous to oral therapy or a total, shorter duration of antibiotic therapy is non-inferior to
prolonged therapy and warrants further study through randomized trials [103, 104••, 105–107].

The decision to use oral therapy depends on pathogen susceptibility to highly bioavailable drugs and patient compliance. Highly bioavailable antimicrobials include fluoroquinolones, metronidazole, clindamycin, linezolid, rifampin, and fluconazole that achieve intrasosseous levels well above the MIC of a targeted organism [108, 109]. Rifampin has excellent antistaphylococcal biofilm activity as demonstrated in animal models and clinical studies. It is recommended for use early on in staphylococcal PJI managed by DAIR or one-stage exchange, always as part of a combination regimen to prevent development of resistance [46••, 97, 109, 110]. Rifampin is not recommended in the absence of hardware (resection arthroplasty), Gram-negative PJI, or chronic suppressive regimens due to risk for hepatotoxicity and drug interactions. In Gram-negative PJI managed by DAIR, the use of fluoroquinolones after initial intravenous therapy has been associated with a good outcome in several studies [107, 111, 112].

Chronic Oral Antimicrobial Suppression

The IDSA guidelines on PJI are unable to provide consensus on the use and duration of chronic suppression following the induction course of intravenous antimicrobial therapy in non-staphylococcal PJI or following the 3- to 6-month course of combination therapy in staphylococcal PJI treated with DAIR. When taking this approach, the adverse effects of long-term antimicrobial use, including emergence of drug-resistant organisms, are major issues to consider. Whether absence or discontinuation of chronic suppression leads to increased risk of treatment failure is still controversial [94, 113•]. The duration of suppression, highest risk period after discontinuation, or a protective effect of suppressive therapy for DAIR alone vs. exchange arthroplasty are all areas of future research. Despite lack of evidence, this approach is frequently utilized in the USA for patients whose comorbidities preclude additional surgery, in cases of treatment failure, immunosuppressed patients, or those with staphylococcal PJI where rifampin was not utilized.

Conclusions

PJI continues to be a significant cause of morbidity after arthroplasty. A high index of suspicion for PJI, early diagnosis, and a logical treatment algorithm that takes host and pathogen factors into consideration affords the best clinical outcome. It is imperative to evaluate existing practices for dental prophylaxis and preoperative asymptomatic bacteriuria in light of scientific evidence advocating against antimicrobial therapy and the growing threat of antimicrobial resistance.

Future areas of research include improvements in diagnostic techniques, duration of antimicrobial therapy, and role of chronic suppression therapy.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that there are no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not describe studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
• Of major importance


