The expanding horizon of prosthetic joint infections

Mayar Al Mohajer[1], Rabih O. Darouiche[2,3]

[1] Department of Medicine, University of Arizona, Tucson, Arizona - USA
[2] Section of Infectious Diseases, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas - USA
[3] Departments of Medicine, Surgery, and Physical Medicine & Rehabilitation, Baylor College of Medicine, Houston, Texas - USA

ABSTRACT

Prosthetic joint infection (PJI) is a serious and potentially devastating complication of arthroplasty. Prior arthroplasty, immunosuppression, severe comorbid conditions, and prolonged surgical duration are important risk factors for PJI. More than half of the cases of PJI are caused by Staphylococcus aureus and coagulase-negative staphylococci. The biofilm plays a central role in its pathogenesis. The diagnosis of PJI requires the presence of purulence, sinus tract, evidence of inflammation on histopathology, or positive microbiologic cultures. The use of diagnostic imaging techniques is generally limited but may be helpful in selected cases. The most effective way to prevent PJI is to optimize the health of patients, using antibiotic prophylaxis in a proper and timely fashion. Management of PJI frequently requires removal of all hardware and administration of intravenous antibiotics. This review summarizes and analyzes the results of previous reports of PJI and assesses the prevention and management of this important entity.

Key words: Prosthetic Joint Infections, Diagnosis, Prevention, Management, Advances

INTRODUCTION

Prosthetic joint replacement surgery (arthroplasty) is considered one of the most successful orthopedic procedures and can lead to pain relief, restoration of function, and improved quality of life in many patients with arthritis (1). It is estimated that 600 000 primary arthroplasties and 70 000 joints revision were done in the United States in 2003. Over 4 million joint surgeries are expected to be performed by the year 2026 (2-3).

Infection of prosthetic joints constitutes a significant, challenging complication of arthroplasty. The rates of prosthetic joint infection (PJI) after primary procedures range from 1% to 9% (<1% in hip and shoulder prostheses, <2% in knee prosthesis, and <9% in elbow prostheses) (4-6). The rates of PJI are significantly higher after revision procedures (<40%) (5). In 2009, the average cost for treating PJI in the United States was $30,300 for primary hip procedures and $93,600 for hip revision procedure (7). The extrapolated annual cost of PJI in the United States alone ranges from $360 million to $730 million (4). Prosthetic joint infections are also associated with high morbidity, the need for repeat surgical procedures, prolonged hospitalization, and occasional death (4-5).

Clinical manifestations and definitions

Joint pain, erythema, swelling, warmth, and fever are all suggestive of PJI but are not specific. Differential diagnosis of PJI should include fracture, dislocation, prosthesis loosening, hemarthrosis, gout, synovitis, and osteolysis (4). Constant pain is suggestive of an infectious etiology, while pain with motion indicates a mechanical process (8).

The Infectious Disease Society of America (IDSA) defines PJI as: A) the presence of a sinus tract communicating with the prosthesis (definite evidence, sensitivity 20-30%, specificity 100%); B) the presence of purulence surrounding the prosthesis without other identifiable causes (definite evidence, sensitivity 20-30%, specificity 100%); C) the presence of acute inflammation on histopathologic exam at the time of surgery (highly suggestive evidence, sensitivity 95-98%, specificity 98-99%); or D) at least two positive intraoperative cultures or a combination of aspiration and intraoperative cultures yielding the same organism (definite evidence, sensitivity 60-85%, specificity 92-97%) (5, 9). The growth of *Staphylococcus aureus* in a single intraoperative culture or a joint aspiration could also represent PJI. It is important to note that PJI can still be present even if all of the above criteria are not

met. Clinical judgment should be used to determine if the patient had PJI after reviewing all pertinent data (9).

PJIs can be classified according to the onset of signs and symptoms after implantation into early infection (within 3 months after surgery), delayed infection (3-24 months) and late infection (>24 months) (3, 5). The infection can be acquired from: A) the surgical wound (perioperative route); B) a distant focus including oral cavity, lung, gut, urinary tract, or skin (hematogenous or lymphogenous route); or C) contiguous foci including soft tissue, osteomyelitis, or septic arthritis (*Per continuitatem* route) (5).

Microbiology

Staphylococcus aureus and coagulase-negative staphylococci (CoNS) are the most common organisms responsible for PJI (~50%) (4, 10). In patients with rheumatoid arthritis, *S. aureus* is the most common pathogen (37%) (11). Polymicrobial infections constitute 20% of cases of PJI (12). Other bacterial pathogens include gram-negative organisms, streptococci, enterococci, and obligate anaerobes. Corynebacteria, propionibacteria, and *Bacillus* spp., which are typically considered contaminants, have been reported to cause PJI (4). *Propionibacterium acne* is a prominent cause of PJI after shoulder arthroplasty (13-14).

Prosthetic joint infections are occasionally caused by fungi (particularly *Candida*) and mycobacteria (*M. tuberculosis* and rapidly growing mycobacteria) (15-19). Occasionally, patients with prior arthroplasty can develop clinical signs and symptoms of PJI without retrieval of organisms from surgical or aspirate specimens. In one study, 7% of cases with PJI were culture negative and had similar outcomes compared to culture positive cases of patients with PJI. Most cases had prior antibiotic therapy (67%) (20).

Pathogenesis

Bacteria are introduced to the joint from the surgical wound during or after the procedure, via hematogenous or lymphogenous route, or by contiguous spread (5). After attachment of bacteria to prosthetic material, they elaborate a fibrous exopolysaccharide material (glycocalyx) creating biofilms (4, 21) (Fig. 1). The formation of biofilms is a critical step for the development of PJI (22). The indwelling metallic prosthesis and polymethylmethacrylate cement lower the amount of bacteria needed to develop an infection and allow microorganisms to persist on their avascular surfaces evading body defenses and systemic antibiotics (4, 23-24). Also, polymethylmethacrylate cement protects microorganisms by disrupting phagocytic, lymphocytic, and complement functions (25).

Planktonic bacteria near the surface of the biofilms are metabolically active and can disseminate through the upper surface of the biofilm with the aid of phagocytic enzymes. Deep bacteria are typically inactive. They are
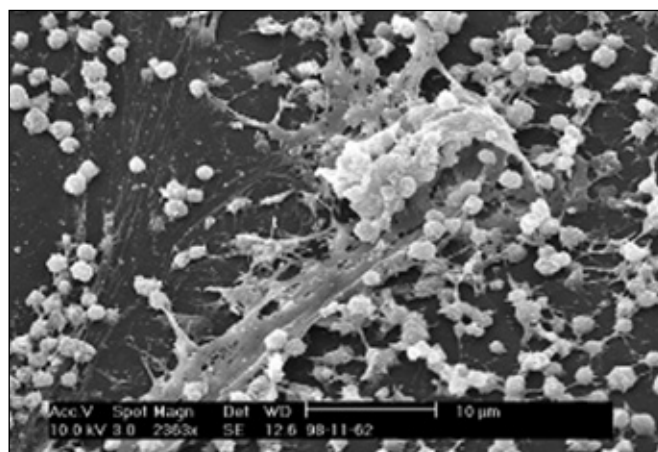

Fig. 1 - *Scanning electron micrograph (SEM) of a Staphylococcus biofilm on the inner surface of a needleless connector. Photograph by Janice Carr, Centers for Disease Control and Prevention, Atlanta, GA USA. From (21): Donlan RM. Biofilms and device-associated infections. Emerg Infect Dis. 2001; 7(2): 277-281.*

protected from phagocytosis and are typically resistant to antimicrobials. Decreased antibiotic penetration, nutrient limitation of biofilm cells, and the adoption of new phenotypes can all explain the inherent resistance of biofilms to antimicrobials (22).

Understanding the role of biofilms in the pathogenesis of PJI can impact both diagnostic and management approaches. Biofilm formation can explain the latency of PJI symptoms after arthroplasty, the difficulty of isolating pathogens from joint aspirates, and the failure of treatment in many patients with prosthesis retention (12).

Risk factors

Several risk factors for PJI have been identified. These include older age, obesity, prior surgeries at the site of prosthesis, rheumatoid arthritis, psoriasis, concurrent malignancies, corticosteroid therapy, recurrent urinary tract infection (UTI), poor nutrition status, and lower socioeconomic status. Additional surgical-related risk factors are perioperative and postoperative nonarticular infections, prior infections of the joint or adjacent bones, prolonged surgery duration, and formation of postoperative hematoma (26-30).

In one case-control study, bacteremia during the previous year, non-surgical trauma to the prosthetic joint, and skin and soft tissue infections were associated with the presence of PJI (31). Another study assessed the risk factors for hip revision due to infection. Male sex, hybrid fixation, using cement without antibiotics, femoral head necrosis, hip fracture, and previous hip inflammatory disease were associated with PJI (32). Nasal colonization with *S. aureus* has been recently proposed as a risk factor for PJI (33). Furthermore, genetic factors may play a role

TABLE I - IMAGING STUDIES USED FOR THE DIAGNOSIS OF PROSTHETIC JOINT INFECTIONS

Study	Advantages	Limitations
Plain x-ray	○ Rule out other causes of chronic pain ○ Baseline for diagnostic and therapeutic procedures	○ Low yield in early and acute PJI ○ Low sensitivity and specificity
Ultrasonography	○ Wildly available ○ Rapidly done ○ Offer guidance for aspiration and drainage ○ No ionizing radiation ○ Helpful in hip infection	○ Operator dependent Low sensitivity and specificity
Computed tomography	○ Guide for aspiration and drainage ○ Helpful in hip infection ○ Can show changes earlier than the X-rays	○ Limited value due to artifact Exposure to ionizing radiation
Magnetic resonance imaging	○ Better image quality than CT	○ Limited value due to artifact Contraindicated in patients with ferromagnetic prosthesis (not commonly used)
Three-phase bone scan (^{99m}TC-labeled diphosphonate)	○ More sensitive than plain X-ray	○ Data inconsistency ○ Low specificity
Sequential bone/gallium scintigraphy	○ Improved specificity compared to bone scan alone ○ Helpful in neutropenic patients	○ High radiation dose ○ Many equivocal cases
In-vitro-labeled leukocytes scan	○ Improved sensitivity and specificity especially when combined with sulfur-colloid bone marrow scan (current imaging of choice)	○ Data inconsistency ○ Not helpful in neutropenic patients ○ Decreased sensitivity in patients pretreated with antibiotics ○ Laborious and expensive
SPECT	○ High specificity ○ Differentiates between soft tissue and joint infections	○ Limited data ○ Limited value due to artifact
FDG-PET	○ High sensitivity ○ Improved resolution	○ Limited data ○ Low specificity ○ Limited value due to artifact Not useful in the first year after arthroplasty ○ Expensive

^{99m}TC = Technetium-99m; SPECT = single photon emission computed tomography; FDG-PET = F-Fluro-deoxyglucose positron emission tomography.

in the development of PJI. One genetic-association study showed that a functional variant of the gene encoding for interleukin-1 beta (IL1B−511*T allele) predisposed to PJI (34).

A National Nosocomial Index score (NNIS) of one or more is associated with PJI (30). One point is added for each of the following variables: A) contaminated or dirty wound; B) duration of operation >75th percentile; and C) severe systemic disease (American Society of Anesthesiologists preoperative score ≥3) (35). The baseline Mayo Prosthetic Joint Infection Risk Score for the development of PJI has been recently proposed to stratify patients undergoing total hip or total knee arthroplasty. This scoring system may be used in targeting preventive strategies in patients undergoing arthroplasty (36).

DIAGNOSIS

Imaging studies

Table I presents different imaging methods used for diagnosis of PJI. Plain x-rays should be performed in all patients with suspected PJI to rule out other causes of joint pain (including fracture and loosening of the prosthesis) and to aid as a baseline for diagnostic and therapeutic procedures (9). They can demonstrate abnormal lucencies at the bone-cement surface, malpositioning of the prosthesis, periosteal reaction, cement fracture, transcortical sinus tract, or prosthesis movement on stress films (4, 9). These radiologic findings are usually late (3-6 months) and non-specific as they can be seen in aseptic processes

(prosthesis fracture and joint dislocation) (37). The use of imaging modalities other than plain x-ray should not be routinely done unless the diagnosis of PJI is unclear and reoperation is not scheduled (9, 38).

Ultrasonography can show fluid collection around the prosthesis and can guide joint aspiration and drainage. It is useful in hip PJI where clinical findings are subtle. It is sometimes difficult to distinguish soft tissue fluid collection from subperiosteal thickening (osteomyelitis) using ultrasonography (40). Computed tomography (CT) may identify subcutaneous abscesses, joint effusions, sinus tracts, bony erosions, and prosthesis loosening (39). Similarly to ultrasonography, CT scans aid in joint aspiration and drainage (40). The use of magnetic resonance imaging (MRI) has been increasing as most recent prosthetic implants are non-ferromagnetic. MRI offers better resolution and can further minimize artifact compared to CT (37, 40).

Radionuclide imaging can be helpful in the diagnosis of PJI but its role is limited due to low specificity. Three-phase bone scintigraphy can show increased uptake of Technetium-99m (^{99m}TC)-labeled diphosphonate on the surface of bone mineral matrix in cases of PJI. However, this can also be seen in cases of sterile inflammation, bone remodeling, fracture, and aseptic prosthetic loosening (37). Sequential bone/gallium scintigraphy technique offers enhanced specificity by comparing spatial distribution congruity of the two scans (41). *In vitro* -labeled leukocytes scan using indium-111(^{111}In) oxyquinolone or ^{99m}TC- hexamethylpropyleneamine oxime (HMPAO) has been associated with improved accuracy of PJI diagnosis (37, 42). The combination of leukocyte scan with sulfur colloid bone marrow scan offers even better results (43). This method has an overall accuracy of 88% to 98% and is the current imaging procedure of choice (9, 40).

Single photon emission computed tomography (SPECT)/CT scan enables more localization of the radio-tracer uptake compared to other radionuclide imaging techniques (44). The specificity of SPECT/CT is markedly increased when combined with leukocyte scanning (45). Fluro-deoxyglucose positron emission tomography (FDG-PET)/CT offers high resolution imaging with excellent sensitivity for the diagnosis of PJI (46). Other investigational methods include the use of ^{99m}TC-interleukin-8, ^{111}In- Biotin scintigraphy, ^{99m}Tc-Ciprofloxacin, ^{99m}Tc-recombinant annexin V scintigraphy, radiolabeled synthetic fragments of ubiquicidin, ^{99m}Tc-labeled bacteriophages (SPECT) and thymidine kinase (PET). These methods may have a prospective role in diagnosis of PJI (37).

Laboratory studies

Testing for white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) is recommended in all patients with suspected PJI (9, 38). These markers are usually elevated in cases of PJI. However, high false-positive rates are not uncommon, particularly after arthroplasty. The utility of using them is improved when normal baseline labs are available (35). Combining ESR and CRP can lead to better accuracy than using either one of them (47). Different cut-offs have been suggested for the diagnosis of PJI (39, 48). Limited data exist regarding the diagnosis utility of procalcitonin, interleukin-6 (IL-6), and soluble intracellular adhesion molecule-1 (sICAM-1) (39).

Microbiologic studies

Blood cultures should be obtained in patients with suspected PJI if they have fever, concomitant infection elsewhere, infection of cardiovascular devices, or if their infection is due to *S. aureus* (9).

The specific diagnosis of PJI often requires isolation of organisms from culture of joint fluid or surgical tissues. Arthrocentesis should be performed in all patients with suspected acute PJI unless the infection is evident, surgery is scheduled, and initiation of antibiotics can be delayed until after surgery (9). Arthrocentesis should also be performed in patients with a chronic painful prosthesis with high clinical suspicion of PJI or with elevated ESR or CRP. Aspirated fluid should be sent for cell count, gram stain, aerobic and anaerobic cultures (9, 38). Withholding antibiotics for medically stable patients for at least two weeks before arthrocentesis or surgery is recommended as it leads to higher yield of identifying the pathogen (9).

The suggested cutoff point for WBC in joint fluid to diagnose PJI is >4200 WBC/µl and >80% polymorphonuclear cells (PMN) for hip joints. This cutoff is lower (>3000 WBC/µl) when combined with elevated ESR and CRP (49). The suggested cutoff point for knee joints is >1700 WBC/µl and >65% PMN (50). One colorimetric chemical strip that detects leukocyte esterase has been shown to be predictive of PJI (sensitivity 80.6%, and specificity 100%). This technique is cheap and provides real-time results, but has limited utility when blood is present in the synovial fluid (51).

Combining intraoperative synovial fluid culture with periprosthetic tissue culture leads to a high sensitivity (90%) and specificity (100%) (52). Obtaining swab cultures is not recommended as it has lower diagnostic yield (39). At least three surgical samples (preferably six) should be obtained and sent for aerobic and anaerobic cultures. Gram stain of tissue specimens has a low sensitivity (9).

Histopathological studies

Histopathological examination of periprosthetic specimens is an important tool for the diagnosis of PJI. The finding of ≥5 neutrophils per high-power field in x40 magnification is indicative of PJI (sensitivity >80% and

specificity >90%) (39). Frozen sections can aid surgeons in deciding whether to perform resection or revision arthroplasty in cases in which perioperative evaluation did not confirm PJI. However, this modality is limited by tissue sampling, and the availability and expertise of the pathologist (9).

Other techniques

The yield of isolating bacteria from biofilm is greater after dislodging them from the explant biofilms using sonication techniques, followed by either culturing or molecular methods (53, 54). Multiplex polymerase chain reaction (PCR) of sonicate fluid is more sensitive in diagnosing PJI (96%) than cultures of sonicate fluid (67%, p=0.016) or periprosthetic tissue (71%, p=0.031) (53). The sensitivity is even greater when combining sonicate fluid PCR with sonicate fluid culture (55, 56). In one study, the sensitivity of combining the two previous tests was reportedly 100%, even in patients who were pretreated with antibiotics (56). Bead-mill process is another novel technique that uses glass beads to agitate and liberate organisms from biofilms. It may shorten time to isolate the organisms and improve the release from biofilms (57).

Automated ribotyping is a rapid and accurate method for diagnosing PJI (58, 59). However, the use of automated ribotyping is limited by the high cost and need for a previous bacterial culture (60, 61). Another recently developed technique is matrix-assisted laser desorption ionization coupled with time of flight analysis mass spectrometry (MALDI-TOF/MS). This technique relies on detecting peptide and protein ions of bacteria through spectra originating from relative charges and masses (61). It can rapidly and reliably identify pathogens responsible for PJI to the species level. Ibis T500 Universal Biosensor (Ibis Biosciences, precursor to the PLEX-ID system; Abbott Laboratories, Chicago, IL, USA) based on PCR-electrospray ionization/mass spectroscopy (PCR-ESI/MS) technique can detect bacteria, viruses, fungi, and protozoa, as well as antimicrobial resistance genes (61, 62). It was evaluated in patients with total knee arthroplasty and was able to detect pathogens in 17/44 (38%) cases of presumed aseptic failure (63).

PREVENTION

Due to the tragic complications of PJI, focusing efforts on prevention should be considered of the highest importance. Table II delineates several key methods for prevention of PJI.

The host

Screening and optimization of patients is an important strategy in preventing PJI (64). Control of dentogingival

TABLE II - STRATEGIES FOR PREVENTION OF PROSTHETIC JOINT INFECTIONS (PJI)

Health optimization	○ Optimizing cardiac function in patients with CAD
	○ Glucose and ulcer control in diabetic patients
	○ Hemoglobin control in anemic patients
	○ Treating gingivitis, obstructing uropathy and control of dermatitis
	○ Screening for nutritional deficiency in cachectic patients, morbidly obese patients and patients with cancer
	○ Counseling for smoking cessation
	○ Cautious use of anticoagulant
	○ Using prognostic tools to assess for risk of PJI
Antibiotic prophylaxis	○ Use of cefazolin, cefuroxime or oxacillin within one hour of surgical incision
	○ Antibiotic discontinuation within 24 hours of surgery
Factors related to surgery	○ Preoperative showering or scrubbing with povidone-iodine, betadine, alcohol, or chlorhexidine-based solutions
	○ Use of plastic adhesive tape or iodine impregnated drapes
	○ Shorter operative time (less than 2.5 hours)
	○ Addition of antibiotics to cement
	○ Surgical tray and instrument sterilization
	○ Decreasing operating room staff
Selected controversial methods	○ Use of filtered laminar flow systems
	○ Use of body-exhaust suits
	○ Use of double gloves
	○ Hair removal with clippers
	○ Changing scalpel blades after skin incision
	○ Adding antibiotics to irrigation solution
	○ Avoidance of postoperative blood transfusion (unless hemoglobin is <8 g/dl)
	○ Urine screening for urinary tract infections
	○ Use of antibiotic prophylaxis before dental, gastrointestinal or genitourinary procedures
	○ Decolonization of MRSA carriers
Future methods	○ Smart implants
	○ Vaccination against *S. aureus*
	○ Biofilm disrupting agents

CAD = Coronary Artery Disease; MRSA = Methicillin-resistant *S. aureus.*
Data modified from (69): Matar WY, Jafari SM, Restrepo C, Austin M, Purtill JJ, Parvizi J.
Preventing infection in total joint arthroplasty. J Bone Joint Surg Am. 2010;92 Suppl 2:36-46.

pathology, obstructive uropathy, and dermatologic conditions before arthrocentesis have been shown to decrease the risk of PJI. Using prognostic tool calculators to assess the risk of PJI can aid surgeons in identifying patients with high risk for treatment failure and to opt for adjusting these factors before arthroplasty (4). Glucose and hemoglobin control, cardiac function optimization, smoking

cessation, and improving nutritional status are vital ways to prevent PJI (64, 65). Screening and treatment of asymptomatic bacteriuria has been attempted with limited data as a method to prevent PJI (66).

Antibiotic prophylaxis

The use of prophylactic antibiotics has been shown to decrease the risk of PJI (relative risk 81%, p<0.001). Cefazolin, cefuroxime, or oxacillin are the antibiotics of choice in most but not all institutions (4, 67). The dose of cefazolin should be increased from 1 g to 2 g for patients who weigh >80 kg. The use of clindamycin or vancomycin is appropriate in patients with previous allergy to beta-lactams. A second dose of cefazolin should be used during prolonged surgeries. Vancomycin is often used in hospitals with high rates of methicillin-resistant *S. aureus* (MRSA) or in patients who have a history of previous MRSA infection or colonization. Antibiotics should be administered within one hour of surgical incision and should not be continued beyond twenty-four hours (68, 69).

The operating room

Several preventive methods related to the operating room are recommended, including preoperative skin preparation, draping, shorter operative time, addition of antibiotics to cement, and controlling the operating room environment (69, 70).

Other methods

As shown in Table II, several controversial methods have been used for prevention of PJI, but more data are needed. Additionally, few innovative approaches have been proposed. Researchers in the field of biomedical sciences have modified implants to overcome bacterial colonization (71-76). These implants are also known as "smart implants" (71, 72). The implantation of copper and silver ions on Ti6AIV4 alloy surfaces has been shown to stimulate osteoblast proliferation and prevent *S. aureus* and *E. coli* colonization (73). Bioglasses doped with gold nanoparticles showed antibacterial properties against *S. aureus* (74). Another approach is modifying implant surfaces to prevent bacterial adhesion. One study showed that using a poly (ethylene glycol)-based monomolecular layer that adsorbs on titanium surfaces was associated with greater stimulation of bone formation and reduction in bacterial adhesion compared to uncoated titanium surfaces (75).

An anti-adhesin vaccination that targets *S. aureus* attachment to biofilms and bacterial invasion into osteoblasts has been attempted in animal studies (77). Unfortunately, the efficacy of these vaccines was limited due to the variable expression of surface proteins on *S. aureus* (78). Other vaccinations that boost Th17 activity or target *S. aureus* protein A (SPA) are under development (79).

Different enzymes have been shown to disrupt biofilms. Studies in vitro and in nematodes showed that deoxyribonuclease (DNAse) can disrupt immature biofilms, increase susceptibility to antibiotics, and increase survival (80). Other studies showed that dispersin B can disrupt biofilms from vascular catheters in vitro, and can decrease catheter colonization in rabbits (81, 82). Extracellular amylase has been shown to prevent biofilm formation by *S. aureus* and *Vibrio cholerae* (83).

MANAGEMENT

Surgical treatment

Surgery is essential in the management of patients with PJI. Multiple surgical options are available, including debridement and retention of the device, one- or two-stage exchange, resection arthroplasty, arthrodesis, and amputation. Many factors can affect the choice of surgery including duration of symptoms, time from arthroplasty, causative organisms and susceptibility pattern, prosthesis loosening, options for reconstructive surgeries, medical comorbidities, surgeon's expertise, and patient's preference (4, 9).

Debridement and retention of the device is a good option for patients who have early PJI (<30 days), short duration of symptoms (<3 weeks), stable prosthesis, and in patients without sinus tract or abscesses (9, 82). Patients with PJI due to MRSA, gram-negative organisms, and patients with *S. aureus* who are not treated with rifampin combination therapy have higher risk of failure when retention of the device is performed (9, 84-86).

A one-stage exchange involves removal of all hardware material and polymethylmethacrylate cement, debridement of bone and soft tissue, and placement of new prosthesis with antibiotic-impregnated cement (9). This procedure is more commonly performed in Europe than in the United States (3). The indications of this procedure include total hip arthroplasty, good soft tissue and bone stock, easily treated organisms, susceptibility to oral antibiotics with high oral bioavailability, use of antibiotic impregnated cement, and no need for bone grafting (85, 87). Advantages include lower morbidity rate and diminished cost (9).

A two-stage exchange is the procedure of choice in the United States for management of chronic PJI with unstable prosthesis. This procedure involves removal of all hardware and cement, debridement, and placement of antibiotic impregnated cement and spacer. Reimplantation of new prosthesis is usually performed from 2 weeks to several months after removal (9). This procedure is

optimal for patients who can tolerate two surgeries and who have adequate bone stock (88). This procedure is a good option for patients with PJI due to MRSA, enterococci, and *Candida* species (9). Reimplantation after four to six weeks of intravenous antibiotics and two to eight weeks of antibiotic-free period are associated with high success rates (89). In cases of infection by less virulent organisms (i.e., excluding MRSA, enterococci or multi-drug resistant gram-negative organisms), reimplantation can be done as early as two to six weeks after hardware removal (1). Decrease in ESR and CRP can aid in deciding the optimal time of reimplantation (9).

Resection arthroplasty or arthrodesis can be performed in nonambulatory patients, patients with limited bone stock, severe comorbidities precluding major surgeries, failed two-staged therapy and those with difficult-to-treat organisms (9). Amputation is indicated in some cases of necrotizing fasciitis, severe bone loss, and previously failed arthroplasty. The functional outcome of amputation is poor (9, 90, 91).

Medical treatment

Rifampin is the mainstay of therapy in patients with PJI due to *S. aureus*, especially in those who underwent retention of the device or one-stage prosthesis exchange (12). Rifampin and fluroquinolone have great biofilm penetration, and this combination has been shown to be associated with high rates of successfully curing infection of retained prostheses (92, 93). Rifampin has also been shown to be active against *P. acne* and *Enterococcus faecalis* in vitro (94, 95). Rifampin should not be used as a monotherapy due to the high likelihood of developing resistance (96).

Fluoroquinolones are also useful in management of PJI (97). However, their efficacy may be limited by induced resistance in vivo, mainly when treating Pseudomonas *aeruginosa* infections (98). For candidal infections, caspofungin is associated with higher biofilm penetration and drastically reduced biofilm dispersion, as compared with fluconazole (99). A summary of IDSA recommendation for medical treatment of PJI is presented in Table III (9).

Novel approaches

Recent studies have reported a promising role of biofilm-disrupting agents in the management of PJI. N-acetylcysteine can disrupt mature biofilms by breaking disulfide bonds, and it has bactericidal effect against several pathogens (100). Using cationic polylysine peptide targeting the polysaccharide intercellular adhesin can decrease biofilm stability by disrupting the charge-charge interaction (101). Another approach is using nanotechnology to maximize local release of antimicrobial agents. Carvacrol, an essen-

TABLE III - ANTIBIOTIC MANAGEMENT OF PROSTHETIC JOINT INFECTIONS

Surgical treatment method	Organisms	Suggested Antibiotic treatment
Debridement and retention of the device or 1-stage exchange	*S. aureus*	○ 2-6 weeks of intravenous antibiotics in combination with oral rifampin or 4-6 weeks of intravenous antibiotics (when rifampin cannot be used)
		○ Followed by rifampin plus an oral antibiotic (FQ preferred) for a total of 3 months (most joints) or 6 months (knee)
		○ Chronic suppressive oral therapy (+/- rifampin) may be considered in selected cases*
	Other than *S. aureus*	○ 4-6 weeks of pathogen-specific intravenous antibiotics or highly active oral therapy
		○ Chronic suppressive oral therapy may be considered in selected cases**
Resection arthroplasty +/- planned stage implantation (2-stage exchange)	Any organism	○ 4-6 weeks of pathogen-specific intravenous antibiotics or highly active oral therapy
Amputation	Any organism	○ 24-48 hours of pathogen-specific antibiotic therapy if all infected bone and soft tissue are amputated
		○ 4-6 weeks of pathogen-specific intravenous antibiotics or highly active oral therapy if there are residual bone of soft tissue infection

FQ = Fluoroquinolone.
*May be used in patients with potential of implant loosening and loss of bone stock, and in those who are unsuitable or refuse further surgeries.
** May be used for infections due to gram-negative organisms after FQ treatment
Modified from (9): Osmon DR, Berbari EF, Berendt AR, et al. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the infectious diseases society of America. Clin Infect Dis. 2013; 56(1): 1-10.

tial oil component, was encapsulated in poly(dl-lactide-coglycolide) nanoparticles. This combination was able to change the elasticity and stability of the biofilm by allowing the delivery of the antibiotic-laden nanoparticles (102). The use of chelating agents such as ethylendiaminetetraacetic acid (EDTA) and desferrioxamine B (DFO) has been associated with decreased growth of *S. aureus* biofilms. However, the use of lower concentration of DFO resulted in an increased biofilm growth (103).

Photodynamic therapy provides a novel way to kill most pathogens (bacteria, fungi, viruses, and protozoa) and it is not affected by microbial resistance. Photoantimicrobials produce reactive oxygen species after they are applied topically and taken up by pathogens. A single

treatment of methylene blue and 670 nanometer non-thermal activating light was associated with >99.9% reduction in MRSA and *P. aeruginosa* biofilms (104).

Laser generated shockwave can deliver non-thermal pulses that remove biofilms. Two studies have shown reduction of bacteria after using shockwave pulses (105, 106). Finally, the use of metabolite profiles can help shed more light on the pathogenesis of PJI, as well as identify new therapeutic properties (107).

CONCLUSIONS

PJI is associated with significant morbidity and mortality. New diagnostic molecular and radiologic techniques have been recently proposed. Modifying implants to incorporate anti-biofilm and antimicrobial agents has a promising future in the field of PJI prevention. The development of biofilm disrupting agents, laser generated shockwave, photodynamic therapies, and metabolomics are new techniques that may aid in management.

Address for correspondence:
Mayar Al Mohajer, MD
Section of Infectious Diseases
Department of Medicine
University of Arizona
1501 N Campbell Avenue
P.O. Box 245039
Tucson, AZ 85724-5039, USA
malmohajer@email.arizona.edu

REFERENCES

1. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004; 351(16): 1645-1654.
2. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am. 2007; 89(4): 780-785.
3. Al Mohajer M, Darouiche RO. Sepsis syndrome, bloodstream infections, and device-related infections. Med Clin North Am. 2012; 96(6): 1203-1223.
4. Brause BD. Infection with Prostheses in Bones and Joints. In: Mandell GL, Bennett JE, Dolin R, (eds). Mandell, Douglas and Bennett's principles and practice of infectious diseases, 7th edition (vol 1). Philadelphia: Elsevier Inc; 2010: 1469-74.
5. Corvec S, Portillo ME, Pasticci BM, Borens O, Trampuz A. Epidemiology and new developments in the diagnosis of prosthetic joint infection. Int J Artif Organs. 2012; 35(10): 923-934.
6. Darouiche RO. Treatment of infections associated with surgical implants. N Engl J Med. 2004; 350(14): 1422-1429.
7. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty. 2012; 27(8 Suppl): 61-5.e1.
8. Gristina AG, Kolkin J. Current concepts review. Total joint replacement and sepsis. J Bone Joint Surg Am. 1983; 65(1): 128-134.
9. Osmon DR, Berbari EF, Berendt AR, et al; Infectious Diseases Society of America. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013; 56(1): 1-10.
10. Del Pozo JL, Patel R. Clinical practice. Infection associated with prosthetic joints. N Engl J Med. 2009; 361(8): 787-794.
11. Berbari EF, Osmon DR, Duffy MC, et al. Outcome of prosthetic joint infection in patients with rheumatoid arthritis: the impact of medical and surgical therapy in 200 episodes. Clin Infect Dis. 2006; 42(2): 216-223.
12. Peel TN, Buising KL, Choong PF. Diagnosis and management of prosthetic joint infection. Curr Opin Infect Dis. 2012; 25(6): 670-676.
13. Kanafani ZA, Sexton DJ, Pien BC, Varkey J, Basmania C, Kaye KS. Postoperative joint infections due to Propionibacterium species: a case-control study. Clin Infect Dis. 2009; 49(7): 1083-1085.
14. Lutz MF, Berthelot P, Fresard A, et al. Arthroplastic and osteosynthetic infections due to Propionibacterium acnes: a retrospective study of 52 cases, 1995-2002. Eur J Clin Microbiol Infect Dis. 2005; 24(11): 739-744.
15. Spinner RJ, Sexton DJ, Goldner RD, Levin LS. Periprosthetic infections due to Mycobacterium tuberculosis in patients with no prior history of tuberculosis. J Arthroplasty. 1996; 11(2): 217-222.
16. Eid AJ, Berbari EF, Sia IG, Wengenack NL, Osmon DR, Razonable RR. Prosthetic joint infection due to rapidly growing mycobacteria: report of 8 cases and review of the literature. Clin Infect Dis. 2007; 45(6): 687-694.

17. Marculescu CE, Berbari EF, Cockerill FR, III, Osmon DR. Fungi, mycobacteria, zoonotic and other organisms in prosthetic joint infection. Clin Orthop Relat Res. 2006; 451: 64-72.

18. Dutronc H, Dauchy FA, Cazanave C, et al. Candida prosthetic infections: case series and literature review. Scand J Infect Dis. 2010; 42(11-12): 890-895.

19. Yilmaz M, Mete B, Ozaras R, et al. Aspergillus fumigatus infection as a delayed manifestation of prosthetic knee arthroplasty and a review of the literature. Scand J Infect Dis. 2011; 43(8): 573-578.

20. Malekzadeh D, Osmon DR, Lahr BD, Hanssen AD, Berbari EF. Prior use of antimicrobial therapy is a risk factor for culture-negative prosthetic joint infection. Clin Orthop Relat Res. 2010; 468(8): 2039-2045.

21. Donlan RM. Biofilms and device-associated infections. Emerg Infect Dis. 2001; 7(2): 277-281.

22. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999; 284(5418): 1318-1322.

23. Zimmerli W, Lew PD, Waldvogel FA. Pathogenesis of foreign body infection. Evidence for a local granulocyte defect. J Clin Invest. 1984; 73(4): 1191-1200.

24. Zimmerli W, Waldvogel FA, Vaudaux P, Nydegger UE. Pathogenesis of foreign body infection: description and characteristics of an animal model. J Infect Dis. 1982; 146(4): 487-497.

25. Petty W. The effect of methylmethacrylate on the bacterial inhibiting properties of normal human serum. Clin Orthop Relat Res. 1978; (132): 266-278.

26. Kurtz SM, Ong KL, Lau E, Bozic KJ, Berry D, Parvizi J. Prosthetic joint infection risk after TKA in the Medicare population. Clin Orthop Relat Res. 2010; 468(1): 52-56.

27. Poss R, Thornhill TS, Ewald FC, Thomas WH, Batte NJ, Sledge CB. Factors influencing the incidence and outcome of infection following total joint arthroplasty. Clin Orthop Relat Res. 1984; (182): 117-126.

28. Jämsen E, Nevalainen P, Eskelinen A, Huotari K, Kalliovalkama J, Moilanen T. Obesity, diabetes, and preoperative hyperglycemia as predictors of periprosthetic joint infection: a single-center analysis of 7181 primary hip and knee replacements for osteoarthritis. J Bone Joint Surg Am. 2012; 94(14): e101.

29. Brause BD. Prosthetic joint infections. Curr Opin Rheumatol. 1989; 1(2): 194-198.

30. Aslam S, Darouiche RO. Prosthetic joint infections. Curr Infect Dis Rep. 2012; 14(5): 551-557.

31. Aslam S, Reitman C, Darouiche RO. Risk factors for subsequent diagnosis of prosthetic joint infection. Infect Control Hosp Epidemiol. 2010; 31(3): 298-301.

32. Dale H, Fenstad AM, Hallan G, et al. Increasing risk of prosthetic joint infection after total hip arthroplasty. Acta Orthop. 2012; 83(5): 449-458.

33. Rao N, Cannella BA, Crossett LS, Yates AJ Jr, McGough RL III, Hamilton CW. Preoperative screening/decolonization for Staphylococcus aureus to prevent orthopedic surgical site infection: prospective cohort study with 2-year follow-up. J Arthroplasty. 2011; 26(8): 1501-1507.

34. Stahelova A, Mrazek F, Smizansky M, Petrek M, Gallo J. Variation in the IL1B, TNF and IL6 genes and individual susceptibility to prosthetic joint infection. BMC Immunol. 2012; 13: 25.

35. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 to June 2002, issued August 2002. Am J Infect Control. 2002; 30(8): 458-475.

36. Berbari EF, Osmon DR, Lahr B, et al. The Mayo prosthetic joint infection risk score: implication for surgical site infection reporting and risk stratification. Infect Control Hosp Epidemiol. 2012; 33(8): 774-781.

37. Gemmel F, Van den Wyngaert H, Love C, Welling MM, Gemmel P, Palestro CJ. Prosthetic joint infections: radionuclide state-of-the-art imaging. Eur J Nucl Med Mol Imaging. 2012; 39(5): 892-909.

38. Parvizi J, Della Valle CJ. AAOS Clinical Practice Guideline: diagnosis and treatment of periprosthetic joint infections of the hip and knee. J Am Acad Orthop Surg. 2010; 18(12): 771-772.

39. Sendi P, Zimmerli W. Diagnosis of periprosthetic joint infections in clinical practice. Int J Artif Organs. 2012; 35(10): 913-922.

40. Palestro CJ, Love C, Miller TT. Infection and musculoskeletal conditions: Imaging of musculoskeletal infections. Best Pract Res Clin Rheumatol. 2006; 20(6): 1197-1218.

41. Merkel KD, Brown ML, Fitzgerald RH, Jr. Sequential technetium-99m HMDP-gallium-67 citrate imaging for the evaluation of infection in the painful prosthesis. J Nucl Med. 1986; 27(9): 1413-1417.

42. Palestro CJ, Love C, Bhargava KK. Labeled leukocyte imaging: current status and future directions. Q J Nucl Med Mol Imaging. 2009; 53(1): 105-123.

43. Reinartz P, Mumme T, Hermanns B, et al. Radionuclide imaging of the painful hip arthroplasty: positron-emission tomography versus triple-phase bone scanning. J Bone Joint Surg Br. 2005; 87(4): 465-470.

44. Weon YC, Yang SO, Choi YY, et al. Use of Tc-99m HMPAO leukocyte scans to evaluate bone infection: incremental value of additional SPECT images. Clin Nucl Med. 2000; 25(7): 519-526.

45. Filippi L, Schillaci O. Usefulness of hybrid SPECT/CT in 99mTc-HMPAO-labeled leukocyte scintigraphy for bone and joint infections. J Nucl Med. 2006; 47(12): 1908-1913.

46. Zhuang H, Yang H, Alavi A. Critical role of 18F-labeled fluorodeoxyglucose PET in the management of patients

with arthroplasty. Radiol Clin North Am. 2007; 45(4): 711-718, vii.

47. Greidanus NV, Masri BA, Garbuz DS, et al. Use of erythrocyte sedimentation rate and C-reactive protein level to diagnose infection before revision total knee arthroplasty. A prospective evaluation. J Bone Joint Surg Am. 2007; 89(7): 1409-1416.

48. Alijanipour P, Bakhshi H, Parvizi J. Diagnosis of Periprosthetic Joint Infection: The Threshold for Serological Markers. Clin Orthop Relat Res. 2013; 471(10): 3186-3195.

49. Schinsky MF, Della Valle CJ, Sporer SM, Paprosky WG. Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty. J Bone Joint Surg Am. 2008; 90(9): 1869-1875.

50. Trampuz A, Hanssen AD, Osmon DR, Mandrekar J, Steckelberg JM, Patel R. Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infection. Am J Med. 2004; 117(8): 556-562.

51. Parvizi J, Jacovides C, Antoci V, Ghanem E. Diagnosis of periprosthetic joint infection: the utility of a simple yet unappreciated enzyme. J Bone Joint Surg Am. 2011; 93(24): 2242-2248.

52. Meermans G, Haddad FS. Is there a role for tissue biopsy in the diagnosis of periprosthetic infection? Clin Orthop Relat Res. 2010; 468(5): 1410-1417.

53. Portillo ME, Salvadó M, Sorli L, et al. Multiplex PCR of sonication fluid accurately differentiates between prosthetic joint infection and aseptic failure. J Infect. 2012; 65(6): 541-548.

54. Trampuz A, Piper KE, Hanssen AD, et al. Sonication of explanted prosthetic components in bags for diagnosis of prosthetic joint infection is associated with risk of contamination. J Clin Microbiol. 2006; 44(2): 628-631.

55. Gomez E, Cazanave C, Cunningham SA, et al. Prosthetic joint infection diagnosis using broad-range PCR of biofilms dislodged from knee and hip arthroplasty surfaces using sonication. J Clin Microbiol. 2012; 50(11): 3501-3508.

56. Achermann Y, Vogt M, Leunig M, Wüst J, Trampuz A. Improved diagnosis of periprosthetic joint infection by multiplex PCR of sonication fluid from removed implants. J Clin Microbiol. 2010; 48(4): 1208-1214.

57. Roux AL, Sivadon-Tardy V, Bauer T, et al. Diagnosis of prosthetic joint infection by beadmill processing of a periprosthetic specimen. Clin Microbiol Infect. 2011; 17(3): 447-450.

58. Campoccia D, Baldassarri L, An YH, et al. Automated ribotyping to distinguish the different non Sau/non Sep staphylococcal emerging pathogens in orthopedic implant infections. Int J Artif Organs. 2006; 29(4): 421-429.

59. Campoccia D, Baldassarri L, Pirini V, Ravaioli S, Montanaro L, Arciola CR. Molecular epidemiology of Staphylococcus aureus from implant orthopaedic infections: ribotypes, agr polymorphism, leukocidal toxins and antibiotic resistance. Biomaterials. 2008; 29(30): 4108-4116.

60. Arciola CR, Montanaro L, Costerton JW. New trends in diagnosis and control strategies for implant infections. Int J Artif Organs. 2011; 34(9): 727-736.

61. Costerton JW, Post JC, Ehrlich GD, et al. New methods for the detection of orthopedic and other biofilm infections. FEMS Immunol Med Microbiol. 2011; 61(2): 133-140.

62. Harris LG, El-Bouri K, Johnston S, et al. Rapid identification of staphylococci from prosthetic joint infections using MALDI-TOF mass-spectrometry. Int J Artif Organs. 2010; 33(9): 568-574.

63. Rasouli MR, Harandi AA, Adeli B, Purtill JJ, Parvizi J. Revision total knee arthroplasty: infection should be ruled out in all cases. J Arthroplasty. 2012 Jun; 27 (6): 1239-43. e1-2.

64. Adeli B, Parvizi J. Strategies for the prevention of periprosthetic joint infection. J Bone Joint Surg Br. 2012; 94 (11 Suppl A): 42-46.

65. Del Savio GC, Zelicof SB, Wexler LM, et al. Preoperative nutritional status and outcome of elective total hip replacement. Clin Orthop Relat Res. 1996; (326): 153-161.

66. Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008; 466(7): 1710-1715.

67. AlBuhairan B, Hind D, Hutchinson A. Antibiotic prophylaxis for wound infections in total joint arthroplasty: a systematic review. J Bone Joint Surg Br. 2008; 90(7): 915-919.

68. Meehan J, Jamali AA, Nguyen H. Prophylactic antibiotics in hip and knee arthroplasty. J Bone Joint Surg Am. 2009; 91(10): 2480-2490.

69. Matar WY, Jafari SM, Restrepo C, Austin M, Purtill JJ, Parvizi J. Preventing infection in total joint arthroplasty. J Bone Joint Surg Am. 2010; 92(Suppl 2): 36-46.

70. Van Staden AD, Dicks LM. Calcium orthophosphate-based bone cements (CPCs): Applications, antibiotic release and alternatives to antibiotics. J Appl Biomater Funct Mater. 2012; 26;10(1): 2-11.

71. Hansen EN, Zmistowski B, Parvizi J. Periprosthetic joint infection: what is on the horizon? Int J Artif Organs. 2012; 35(10): 935-950.

72. Arciola CR, Campoccia D, Speziale P, Montanaro L, Costerton JW. Biofilm formation in Staphylococcus implant infections. A review of molecular mechanisms and implications for biofilm-resistant materials. Biomaterials. 2012; 33(26): 5967-5982.

73. Fiedler J, Kolitsch A, Kleffner B, Henke D, Stenger S, Brenner RE. Copper and silver ion implantation of aluminium oxide-blasted titanium surfaces: proliferative response of osteoblasts and antibacterial effects. Int J Artif Organs. 2011; 34(9): 882-888.

74. Grandi S, Cassinelli V, Bini M, et al. Bone reconstruction: Au nanocomposite bioglasses with antibacterial properties. Int J Artif Organs. 2011; 34(9): 920-928.

75. Bozzini S, Petrini P, Tanzi MC, Arciola CR, Tosatti S, Visai L. Poly (ethylene glycol) and hydroxy functionalized alkane phosphate self-assembled monolayers reduce bac-

terial adhesion and support osteoblast proliferation. Int J Artif Organs. 2011; 34(9): 898-907.

76. Baino F, Fiorilli S, Mortera R et al. Mesoporous bioactive glass as a multifunctional system for bone regeneration and controlled drug release. J Appl Biomater Funct Mater. 2012; 26;10(1): 12-21.

77. Testoni F, Montanaro L, Poggi A, Visai L, Campoccia D, Arciola CR. Internalization by osteoblasts of two Staphylococcus aureus clinical isolates differing in their adhesin gene pattern. Int J Artif Organs. 2011; 34(9): 789-798.

78. Brady RA, O'May GA, Leid JG, Prior ML, Costerton JW, Shirtliff ME. Resolution of Staphylococcus aureus biofilm infection using vaccination and antibiotic treatment. Infect Immun. 2011; 79(4): 1797-1803.

79. Spellberg B, Daum R. A new view on development of a Staphylococcus aureus vaccine: insights from mice and men. Hum Vaccin. 2010; 6(10): 857-859.

80. Kaplan JB, LoVetri K, Cardona ST, et al. Recombinant human DNase I decreases biofilm and increases antimicrobial susceptibility in staphylococci. J Antibiot (Tokyo). 2012; 65(2): 73-77.

81. Kaplan JB, Ragunath C, Velliyagounder K, Fine DH, Ramasubbu N. Enzymatic detachment of Staphylococcus epidermidis biofilms. Antimicrob Agents Chemother. 2004; 48(7): 2633-2636.

82. Darouiche RO, Mansouri MD, Gawande PV, Madhyastha S. Antimicrobial and antibiofilm efficacy of triclosan and DispersinB combination. J Antimicrob Chemother. 2009; 64(1): 88-93.

83. Kalpana BJ, Aarthy S, Pandian SK. Antibiofilm activity of α-amylase from Bacillus subtilis S8-18 against biofilm forming human bacterial pathogens. Appl Biochem Biotechnol. 2012; 167(6): 1778-1794.

84. Marculescu CE, Berbari EF, Hanssen AD, et al. Outcome of prosthetic joint infections treated with debridement and retention of components. Clin Infect Dis. 2006; 42(4): 471-478.

85. Salgado CD, Dash S, Cantey JR, Marculescu CE. Higher risk of failure of methicillin-resistant Staphylococcus aureus prosthetic joint infections. Clin Orthop Relat Res. 2007; 461: 48-53.

86. Hsieh PH, Lee MS, Hsu KY, Chang YH, Shih HN, Ueng SW. Gram-negative prosthetic joint infections: risk factors and outcome of treatment. Clin Infect Dis. 2009; 49(7): 1036-1043.

87. Jackson WO, Schmalzried TP. Limited role of direct exchange arthroplasty in the treatment of infected total hip replacements. Clin Orthop Relat Res. 2000; (381): 101-105.

88. Matthews PC, Berendt AR, McNally MA, Byren I. Diagnosis and management of prosthetic joint infection. BMJ. 2009 May 29; 338: b1773.

89. Toulson C, Walcott-Sapp S, Hur J, et al. Treatment of infected total hip arthroplasty with a 2-stage reimplantation protocol: update on "our institution's" experience from 1989 to 2003. J Arthroplasty. 2009; 24(7): 1051-1060.

90. Isiklar ZU, Landon GC, Tullos HS. Amputation after failed total knee arthroplasty. Clin Orthop Relat Res. 1994; (299): 173-178.

91. Fedorka CJ, Chen AF, McGarry WM, Parvizi J, Klatt BA. Functional ability after above-the-knee amputation for infected total knee arthroplasty. Clin Orthop Relat Res. 2011; 469(4): 1024-1032.

92. Widmer AF, Frei R, Rajacic Z, Zimmerli W. Correlation between in vivo and in vitro efficacy of antimicrobial agents against foreign body infections. J Infect Dis. 1990; 162(1): 96-102.

93. Senneville E, Joulie D, Legout L, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to Staphylococcus aureus. Clin Infect Dis. 2011; 53(4): 334-340.

94. Furustrand Tafin U, Corvec S, Betrisey B, Zimmerli W, Trampuz A. Role of rifampin against Propionibacterium acnes biofilm in vitro and in an experimental foreign-body infection model. Antimicrob Agents Chemother. 2012; 56(4): 1885-1891.

95. Holmberg A, Mörgelin M, Rasmussen M. Effectiveness of ciprofloxacin or linezolid in combination with rifampicin against Enterococcus faecalis in biofilms. J Antimicrob Chemother. 2012; 67(2): 433-439.

96. Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. Clin Microbiol Rev. 2010; 23(1): 14-34.

97. Widmer AF, Wiestner A, Frei R, Zimmerli W. Killing of nongrowing and adherent Escherichia coli determines drug efficacy in device-related infections. Antimicrob Agents Chemother. 1991; 35(4): 741-746.

98. Trampuz A, Zimmerli W. Diagnosis and treatment of implant-associated septic arthritis and osteomyelitis. Curr Infect Dis Rep. 2008; 10(5): 394-403.

99. Uppuluri P, Srinivasan A, Ramasubramanian A, Lopez-Ribot JL. Effects of fluconazole, amphotericin B, and caspofungin on Candida albicans biofilms under conditions of flow and on biofilm dispersion. Antimicrob Agents Chemother. 2011; 55(7): 3591-3593.

100. Aslam S, Darouiche RO. Role of antibiofilm-antimicrobial agents in controlling device-related infections. Int J Artif Organs. 2011; 34(9): 752-758.

101. Hofmann CM, Bednar KJ, Anderson JM, Marchant RE. Disruption of Staphylococcus epidermidis biofilm formation using a targeted cationic peptide. J Biomed Mater Res A. 2012; 100(4): 1061-1067.

102. Iannitelli A, Grande R, Di Stefano A, et al. Potential Antibacterial Activity of Carvacrol-Loaded Poly(DL-lactide-co-glycolide) (PLGA) Nanoparticles against Microbial Biofilm. Int J Mol Sci. 2011; 12(8): 5039-5051.

103. Al-Azemi A, Fielder MD, Abuknesha RA, Price RG. Effects of chelating agent and environmental stresses

on microbial biofilms: relevance to clinical microbiology. J Appl Microbiol. 2011; 110(5): 1307-1313.

104. Wainwright M. Photodynamic medicine and infection control. J Antimicrob Chemother. 2012; 67(4): 787-788.

105. Taylor ZD, Navarro A, Kealey CP, et al. Bacterial biofilm disruption using laser generated shockwaves. Conf Proc IEEE Eng Med Biol Soc. 2010; 2010: 1028-32.

106. Kizhner V, Krespi YP, Hall-Stoodley L, Stoodley P. Laser-generated shockwave for clearing medical device biofilms. Photomed Laser Surg. 2011; 29(4): 277-282.

107. Cohen MJ, Serkova NJ, Wiener-Kronish J, Pittet JF, Niemann CU. 1H-NMR-based metabolic signatures of clinical outcomes in trauma patients—beyond lactate and base deficit. J Trauma. 2010; 69(1): 31-40.