

SUPPLEMENT ARTICLE

New Developments in Diagnosis and Treatment of Infection in Orthopedic Implants

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Orthopedic implants have revolutionized treatment of bone fractures and noninfectious joint arthritis. Today, the risk for orthopedic device–related infection (ODRI) is <1%–2%. However, the absolute number of patients with infection continuously increases as the number of patients requiring such implants grows. Treatment of ODRI most frequently includes long-term antimicrobial treatment and removal of the implant. Recent evidence from observational trials and 1 randomized clinical trial indicate that a subset of patients can be successfully treated with retention of the implant. Patients eligible for such a treatment must meet the following criteria: acute infection defined as signs and symptoms lasting <14–28 days, an unambiguous diagnosis based on histopathology and microbiology, a stable implant, and susceptibility of the microorganism to an effective orally available antimicrobial agent.

Orthopedic implants have become an essential component of modern medicine. More than 200,000 total hip replacements are performed annually in the United States and >50,000 in the United Kingdom [1]. The safety and biocompatibility of these devices are excellent, and <10% of the patients at risk experience complications during their lifetime [2]. Arthroplasty has become the treatment of choice for patients aged ≥ 55 years with severe pain and disability from knee arthritis [3]. Because the percentage of patients aged >65 years is on the rise in industrialized countries, the number of patients requiring implants will continue to grow, as will the risk for orthopedic device–related infections (ODRIs). In the United States, >4.4 million people have at least 1 internal fixation device and >1.3 million have an artificial joint [4].

Sophisticated prevention strategies have been developed during the past 2 decades to lower the risk of infectious complications in implant surgery. Examples include laminar airflow with ultraclean air [5], routine

antimicrobial prophylaxis [6], short operating time, use of antibiotic-bonded cement [7], and antimicrobial coating [8, 9]. Although incidence of ODRI is now low—internationally <1%–2% in institutions with highly trained surgeons [10]—even a very low risk of infection can result in a number of patients with ODRI. Such patients are mainly treated at the institution where the prosthesis had been implanted. The scarcity of infections per institution may explain why treatment of such an infection is poorly standardized. Randomized controlled clinical trials are hampered by the fact that only large institutions have sufficient numbers of patients to enroll and that successful treatment requires a follow-up of >2 years. Therefore, such studies frequently lack appropriate statistical power because of patients being lost to follow-up, changing residence, or dying of underlying diseases. The publication of such a study took 6 years from design until results from the 2-year follow-up were available [11]. Moreover, diagnosis and management require close collaboration between surgeons, infectious disease specialists, microbiologists, and pathologists, and internationally accepted criteria for diagnosis and consecutive treatment of ODRI have not been developed. Therefore, the diagnosis refers more to surgical criteria in studies conducted by surgeons and relies predominantly on microbiological data in studies

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guided by microbiologists. Not surprisingly, the various criteria for diagnosis and multifaceted approaches for treatment have led to diverse conclusions and recommendations.

Simple surgical drainage with retention of the prosthesis in situ and treatment with antimicrobial agents have been associated with failure rates of 60%–80% [12, 13]. However, more recent studies have cited failure rates of <20% when a standardized protocol for salvage treatment was used [11, 14, 15]. A nonoperative or minimally invasive surgical approach is attractive for both patient and clinician, especially because most patients with prosthetic joints are elderly and have significant comorbidities. Proper selection of patients allows successful treatment of infection, with salvage of the implant. However, careful evaluation of the patients, their underlying diseases, the type of implant, the quality of the bone stock, and an unambiguous diagnosis of infection are prerequisites for successful management of such infections. Appropriate treatment achieves cure rates of >80% with retention of the device, reducing morbidity, mortality, and cost of treatment of ODRIs. Nevertheless, only a subset of patients qualifies. In general, infections associated with internal fixation devices rather than joint prostheses respond better to salvage. Infections associated with total knee prostheses are more difficult to manage than are those associated with total hip prostheses. This review focuses on new developments in diagnosis and treatment of ODRIs, with emphasis on strategies of retaining the device.

PATHOGENESIS OF ODRIs

Biofilm formation. The pathogenesis of ODRIs has been reviewed elsewhere and is beyond the scope of this review [16]. However, an understanding of the pathogenesis of biofilm formation facilitates optimal diagnosis and treatment. In addition, it explains why signs and symptoms are relieved by short-term treatment with antimicrobial agents but reoccur immediately after withdrawal of treatment [17]. All implants undergo physiological changes after implantation. The earliest and probably clinically the most important step is the “race for the surface,” a contest between tissue cell integration and bacterial adhesion to that same surface [18]. On contact, body fluids immediately coat all surfaces with a layer of host material, primarily serum proteins and platelets. Albumin, as the major serum component, is rapidly deposited on foreign material and prevents nonspecific neutrophil activation and deposition of matrix proteins on the surfaces [19]. Adherence of *Staphylococcus aureus* to bioprosthetic materials is mediated by adhesins, such as fibronectin, fibrinogen, fibrin, collagen, laminin, vitronectin, thrombospondin, bone sialoprotein, elastin, and the matrix-binding protein. These host proteins promote attachment of *S. aureus* onto polymeric or metallic surfaces by specific receptors. Such mechanisms are ill-defined for coagulase-negative staph-

ylococci (CNS), because most studies are done in the absence of proteins [20]. Adherence progresses to aggregation of microorganisms on the surface of the foreign body, forming a biofilm. As the colonies mature, sessile bacteria on the periphery detach and disperse as planktonic bacteria. This process can lead to clinically overt infection but rarely to bacteremia. Costerton et al. [21] defined bacterial biofilms as “structured communities of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface.” Both types of surfaces are frequently present in ODRIs: the medical device and sequestra of dead bone. Biofilms grow slowly and can resist cellular and humoral immune responses [22]. Moreover, several mechanisms render biofilm bacteria less susceptible to antimicrobial agents than their planktonic counterparts. Cell-to-cell signals, involved in the development of the bacterial biofilm in *Pseudomonas aeruginosa*, may provide a new target to control biofilm formation, but they have not yet been documented for other bacteria [23]. Clinically established mechanisms include adherence of bacteria, slime production, and slow rate of bacterial growth. Bacteria become sessile in the biofilm, and their phenotypic features change considerably. They become resistant through several mechanisms that are still a major topic of research. The 2 clinically important mechanisms are failure of antimicrobial agents to penetrate the biofilm and the stationary phase of growth. In addition, some bacteria, such as *S. aureus*, form small-colony variants, characterized by reduced growth rate, diminished exoprotein production, decreased susceptibility to aminoglycosides, and possible intracellular persistence [24]. Standard antibiotic therapy typically reverses signs and symptoms caused by planktonic bacteria released from the biofilm but fails to kill bacteria in the biofilm [21]. Therefore, successful treatment of ODRIs with retention of the implant incorporates treatment against both planktonic and sessile bacteria. Another option is to kill planktonic bacteria by antimicrobial agents and to get rid of sessile bacteria by removing the implant [21].

Slime production. A variety of microorganisms, particularly CNS but also *P. aeruginosa* and *Streptococcus mutans*, develop slime, an amorphous extracellular glycolcaliceal substance based on polysaccharide. Electron microscopy clearly shows implants quickly covered by several layers of slime. Slime production is usually triggered by adherence to surfaces but is also a property of a particular strain. Many strains of CNS isolated from clinically significant infections exude slime. Slime extracted from CNS grown on chemically defined medium consists of 80% teichoic acid and 20% protein [25]. Glycocalyx promotes intercellular adhesion, captures nutrients, and protects microorganisms from the deleterious effects of antimicrobial agents. Many investigators consider slime a virulence factor, because strains of CNS from prosthetic valve endocarditis are more likely to produce it than are those not cultured

from such infections [26]. Christensen et al. [27] clearly showed that slime-producing CNS are more likely to be isolated from a device than from random blood cultures. However, its production appears as a heterogeneous phenomenon in which there is unequal expression of slime by individual daughter cells from the same strain. Slime has potent immunomodulatory properties and alters the susceptibility of the microorganisms to antimicrobial agents. Slime can decrease chemotaxis and opsonization of neutrophil granulocytes, increase degranulation, and block penetration of antibiotics into the bacterial cell [28].

Mode of growth. Bacteria in a biofilm do not grow exponentially. They exist in a slow-growing or starved state (i.e., stationary phase) [21]. Studies of ODRIs in an animal model confirmed the slow-growing or starved state of bacterial growth for *S. aureus* and *Escherichia coli*. The MICs determined according to recommendations by the National Committee for Clinical Laboratory Standards do not accurately reflect conditions observed in ODRIs [29]. In addition, standard susceptibility testing measures the inhibitory activity of an antimicrobial agent, but bactericidal activity appears to be fundamental for successful treatment of ODRIs. Attempts have been made to improve routine susceptibility testing by measuring MBCs, kill curves, and serum bactericidal titers. These methods test planktonic bacteria in logarithmic phase of growth but are difficult to interpret. MBCs are defined as $\geq 99.9\%$ killing. A very few organisms (usually $< 0.1\%$ of the final inoculum) survive the lethal effect of an antibiotic, even if they turn out to be highly responsive to standard susceptibility testing. This phenomenon is thought to result from the fact that some cells are dormant or replicating slowly and, consequently, are not killed by the antibiotic, a situation quite similar to the conditions observed in ODRIs.

Therefore, we performed susceptibility testing in parallel with exponentially growing bacteria and bacteria in a slow-growing state to better simulate conditions observed in ODRIs. Much higher concentrations were needed to kill stationary-phase bacteria than logarithmically growing bacteria [30, 31], and several investigators confirmed these findings [21, 32, 33]. Costerton et al. [34] and the National Committee for Clinical Laboratory Standards proposed guidelines in the early 1990s to test antimicrobial efficacy against stationary-phase bacteria. They called it “biofilm-eliminating concentration,” or BEC. In our model [30, 31], killing depended not only on the antimicrobial agent but also on the microorganism. Rifampin alone was highly effective against stationary-phase gram-positive cocci such as *Staphylococcus epidermidis* and *S. aureus*. Moreover, the MBC of rifampin determined for stationary-phase bacteria remained in a range achievable in serum and tissue with a standard dosage of rifampin in humans. The MBCs of ciprofloxacin increased 200 times when tested with stationary-phase *S. epidermidis*. In

contrast, ciprofloxacin was highly efficacious against stationary-phase *Salmonella dublin* and *E. coli* ATCC 25922. These observations are supported by experiments by Zeiler and colleagues [33, 35] and other investigators [30, 31]. They also showed good activity of ciprofloxacin against stationary-phase bacilli such as *E. coli*. The mode of action remains unclear, but these tests correlated much better with the results of the guinea pig model and human studies than did routine susceptibility testing and regular MBCs [30, 31].

Why some antimicrobial agents perform better than others against stationary-phase bacteria is poorly understood. The reduced efficacy of β -lactam antibiotics may be explained in part by their primary mode of action. Their killing is growth-dependent, and, hence, slow-growing bacteria in device-related infections are not as affected as those growing logarithmically in the laboratory. However, other complex interactions, including slime production, can inhibit antimicrobial activity of, for example, glycopeptides [36]. More research is needed to clarify the role of slime in the pathogenesis of device-related infections. Results of several authors indicate that an antimicrobial agent should be bactericidal against slow-growing bacteria for optimal effectiveness [11, 30, 33]. In general, a 10–100-times higher concentration than the MIC is required to achieve this desired activity, but success also depends on species, strain, and antimicrobial agent.

NOMENCLATURE OF ODRIS

As mentioned above, an internationally accepted classification for ODRIs has not yet been established. Such a classification could guide the management of these infections and facilitate the comparison of approaches from different institutions. Conventry [37] proposed a frequently used classification (table 1), which has been adapted by reducing the time frame for early infection from 3 months to 1 month [38]. Current clinical evidence indicates that with immediate treatment of acute infection (< 2 weeks after onset of signs or symptoms), the implant can be salvaged [11, 12, 39]; therefore, the current classification should probably be adapted to define early postoperative infections as occurrence of signs or symptoms from < 14 days to a maximum of 28 days after surgery (table 1). The best evidence is based on a randomized clinical trial: All patients who were able to complete the treatment plan and began treatment within < 1 week of clinical onset were cured [11]. Other groups supported these data with retrospective studies [2, 12, 13, 40]. Tsukayama et al. [40] included a group of patients with “intraoperative positive cultures,” who were operated on with the presumptive diagnosis of aseptic loosening of the device without signs or symptoms of infection. Routine cultures unexpectedly revealed at least 2 positive specimens with the same microorganism. Because CNS were isolated in 71% of these

Table 1. Nomenclature of orthopedic device–related infections.

Infection category	Typical onset after surgery	Type	Signs and symptoms	Representative microorganism
Early postoperative	≤2–4 weeks	Acute (type I)	Persistent pain after surgery, fever, redness, swelling after surgery	<i>Staphylococcus aureus</i> , coagulase-negative staphylococci
Late chronic	≥1 month	Chronic (type II)	Insidious onset, persisting pain after surgery	Coagulase-negative staphylococci, <i>Propionibacterium</i> species, anaerobes, <i>S. aureus</i>
Hematogenous	>2 years	Acute (type III)	Fever, pain, redness, swelling after a long period of wellness	Streptococci, <i>S. aureus</i> , gram-negative bacilli

cases, indicating low-grade chronic infection, these patients should be included in the group of chronic infection with low-virulence pathogens.

Early postoperative infections. These occur in the immediate postoperative period, representing a classic surgical site infection [41] as defined by the Centers for Disease Control and Prevention. The patient usually presents with fever, chills, and sweating. Pain persists in the early postoperative period and does not decline as in noninfected patients. The wound may be erythematous, swollen, fluctuant, and tender. A diagnostic challenge is the distinction between a superficial infection and the contiguous infection deep to the fascia and around the implant [2]. Empirical treatment with antimicrobial agents may mitigate signs or symptoms of infection but will ultimately result in chronic infection and is not recommended. Therefore, such patients require a rapid workup for suspected early infection and qualify for implant salvage given the circumstances listed in table 2.

Late chronic infection. Chronic infections likely originate at the time of surgery. A very low inoculum or a low-virulence pathogen such as CNS delays the onset of clinically apparent infection and does not trigger symptoms of acute infection. The typical onset of this type of infection is between 16 months and 2 years [10]. The hallmark is gradual deterioration in function and concurrent intensifying pain. Early loosening of the implant may be the only symptom of chronic infection in patients with a joint prosthesis. The distinction between aseptic loosening of a prosthesis and low-grade chronic infection remains a challenge despite advances in diagnostic tools. Such an infection responds poorly to treatment with antimicrobial agents with retention of the device, even after extensive debridement.

Hematogenous infection. The hallmark of this type of infection is a sudden, rapid deterioration in the function of an implant that was functioning well for a long period after surgery [10]. It occurs almost exclusively in joint prostheses. Most infections are observed >2 years after surgery, presenting with signs and symptoms similar to early postoperative infection. Hematogenous seeding may be triggered by dental manipulation, catheter-associated urinary tract infection and urosepsis,

and remote infection. Not surprisingly, streptococci are more frequently isolated in this type of infection than in others. Patients at risk for hematogenous seeding are those under immunosuppression for inflammatory arthropathy or transplant patients. Immediate workup of patients with these signs or symptoms is crucial. Such an infection may also qualify for salvage treatment.

MICROORGANISMS IN ODRIs

Staphylococci are the most frequently encountered microorganisms isolated from patients with ODRIs (table 3), accounting for ~50% of the cases [44]. Others are anaerobes, gram-negative bacilli such as *Pseudomonas* species or *E. coli*, and, especially in hematogenous infections, streptococci [2, 13]. Tunney et al. [45] isolated *Propionibacterium* species in 60% of ODRIs by using strict anaerobic bacteriologic practices during the processing of samples considered associated with ODRIs. *Propionibacterium* species are the second most frequent contaminant observed in joint aspiration [46]. Multiple organisms are frequently isolated from such samples, which may indicate polymicrobial infection but raises the possibility that one microorganism may be responsible for infection and the other may be a contaminant. Molecular diagnostic tools will likely render the interpretation of microbiological results even more difficult. How-

Table 2. Criteria for patients to be considered for treatment of orthopedic device–related infections with salvage of implant.

Criterion
Acute infection with signs and symptoms of ≤14–28 days
Stable implant with no signs or symptoms of loosening
Clearly established diagnosis by isolating single microorganism from multiple specimens by aspiration or preferably intraoperative culture during debridement
Positive histopathologic results, preferably by frozen section
Pathogen susceptible to oral, preferably bactericidal, antimicrobial agent
Antimicrobial agent with proven effectiveness in preferably human (see table 5) or animal studies
Patient able and willing to undergo long-term antimicrobial therapy

Table 3. Microorganisms isolated from orthopedic device-related infections.

Microorganism	%
Coagulase-negative staphylococci	20–25
<i>Staphylococcus aureus</i>	20–25
Polymicrobial	14–19
Gram-negative bacilli	8–11
Streptococci	8–10
Anaerobes ^a	6–10
Enterococci	3
Other	10

^a Positive anaerobic culture depends on transport media used in operating room and microbiological technique.

ever, multiple specimens for culture should be taken from any suspected infection site, and the clinician should put samples in transport media for anaerobic microorganisms. Results of multiple specimens will facilitate interpretation of the culture results. A single positive result for a particular microorganism from culture of 3 specimens of skin usually signifies contamination, whereas presence of an organism in all 3 specimens, even *Propionibacterium* species, indicates infection. Additional information from the microbiology laboratory may help to suggest true infection, such as short time to positivity, massive growth in cultures, and the resistance pattern of the pathogen. For example, isolation of a penicillin-susceptible CNS endorses a diagnosis of contamination, because most CNS are penicillin-resistant. However, some cases remain unclear even after reviewing all clinical, microbiological, and histological data available. The high likelihood of contamination precludes the routine use of microbiological culture for ODRI without clinical signs or symptoms of infection, unless multiple specimens are taken for microbiology and histopathology. Nevertheless, some patients scheduled for routine replacement do not present with overt signs or symptoms of infection, and diagnosis of ODRI is made exclusively by intraoperative culture and histopathology. This applies specifically to patients with suspected diagnosis of aseptic loosening of the implant, who require a very careful workup.

DIAGNOSTIC WORKUP

No preoperative tests are consistently sensitive and specific for infection in patients who need a revision arthroplasty. Interpretation of the investigative tests are easier for internal fixation devices than for joint prostheses. Definitive diagnosis based solely on history and physical findings may prove inaccurate. However, a careful history of the patient and risk assessment is mandatory for all patients with evidence of ODRI. A recent case-control study clearly established several risk factors for the development of ODRI in patients with prosthetic joints. The

most important was a postoperative surgical site infection (OR, 35.9) [41], followed by a high NNIS (National Nosocomial Infections Surveillance) system score (OR, 3.9), systemic malignancy (OR, 3.1), and prior joint arthroplasty (OR, 2.0) [42]. Knee arthroplasties are associated with a higher risk of infection (2%) than hip arthroplasties (1.3%) [47], as are, in general, revision procedures [47]. Although these data are epidemiologically important, they are of little help in evaluating the individual patient with an implant. The only consistent clinical finding in ODRI is pain at the site of the implant. Hematologic testing results, erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) levels, and x-rays and bone scan results are highly variable. In addition, the sensitivity of standard microbiological cultures does not exceed 70% [48]. Only the sum of clinical signs and symptoms, blood tests, radiography, bone scans, and a microbiological workup can provide an accurate diagnosis. However, a score to ultimately establish the diagnosis has not been widely used. Therefore, one should know about the impact of a positive test to rule out or support the diagnosis of ODRI. Clinicians typically weigh multiple clinical signs and symptoms, laboratory findings, and radiographic results in a nonstandardized fashion before diagnosing a case of ODRI.

The likelihood ratio (LR) determines the performance of a test in a standardized fashion. It expresses the ratio of the chance that a given diagnostic test result would be observed for a patient with the target disease relative to the chance that it would be observed for a patient without the disease [49]. The LR positive is calculated as follows: sensitivity/(1 – specificity). The LR negative is determined as follows: (1 – sensitivity)/specificity. Pretest odds are estimated by the following equation: pretest probability/(1 – pretest probability). Posttest odds are computed by multiplying the pretest odds by the LR positive or negative, respectively. The posttest odds convert back into posttest probability by the following relationship: probability = odds/(1 + odds). Tests with an LR positive of ≥ 10 or an LR negative of 0.1 are considered excellent. Table 4 summarizes estimated LRs for various tests based on published studies cited in MEDLINE between 1975 and 2000. Calculation is facilitated by using a nomogram available from multiple sources (e.g., <http://cebm.jr2.ox.ac.uk/docs/nomogram.html>). For example, a clinician evaluates a patient with suspected ODRI. Presence of a normal ESR and CRP level basically rules out the presence of ODRI. Clinical evaluation may provide evidence that a patient has ODRI, with a pretest probability of up to 50%, translating to odds of 1:1. The posttest odds for a normal ESR is calculated by multiplying the pretest odds (1) times the LR negative (0.18), resulting in 0.18. The posttest probability, $0.18/(1 + 0.18)$, is converted into a 15% probability that the patient has the disease. The same calculation is repeated with the normal CRP value, which provides a negative LR of

Table 4. Likelihood ratios (LRs) for tests evaluating orthopedic device-related infections (ODRIs).

Category, test or finding	Sensitivity, median (range)	Specificity, median (range)	LR positive	LR negative	Comment	References
Clinical and laboratory						
ESR >30 mm/h ^a	0.83 (0.61–0.96)	0.9 (0.79–1)	8.3	0.18	May be elevated because of underlying disease (e.g., rheumatoid arthritis)	[50–53]
C-reactive protein level >10 mg/L	0.95 (0.91–0.96)	0.9 (0.88–0.92)	9.5	0.05	Similar to ESR but decreases rapidly after surgery in noninfected patients	[51, 54]
Clinical assessment	0.7	0.87	5.3	0.34	Intraoperative clinical impression of surgeon	[55]
Nuclear imaging						
Technetium/gallium scanning	0.44 (0.38–0.5)	0.86 (0.78–1.0)	3.4	0.67	Expensive, low accuracy	[56–58]
Technetium/indium 111-labeled WBC scanning	0.94 (0.38–1.0)	0.94 (0.41–1.0)	15	0.06	Results biased because sequential scanning improved accuracy, may also be inconclusive	[59–63]
Indium 111-labeled IgG scanning	0.97 (0.91–1.0)	0.82 (0.5–1.0)	6.4	0.03	Results similar to WBC scanning, but no WBC preparation and phlebotomy necessary	[64–67]
Histopathology						
Frozen section from intraoperative samples of periprosthetic tissue	0.82 (0.18–1.0)	0.96 (0.90–0.99)	20	0.18	Experienced pathologist required	[50, 55, 68–71]
Microbiology						
Microscopy						
Gram staining of intraoperative samples	0.17 (0.0–0.23)	0.98 (0.9–0.99)	8.5	0.84	Only positive results useful	[45, 54–56, 72]
Immunofluorescence microscopy	0.63 (NA)	0.47 (NA)	1.2	0.78		[45]
Culture ^a						
Preoperative aspiration ^b	0.86 (0.5–0.93)	0.92 (0.82–0.97)	10.8	0.15	Antibiotics should be stopped before aspiration; additional synovial biopsies are helpful, especially in dry taps	[43, 46, 50, 52, 56, 73–77]
Intraoperative culture ^a	1.0 ^b (0.83–1.0)	0.86 (0.87–0.9)	>7 ^c	<0.01 ^c		[74]

NOTE. ESR, erythrocyte sedimentation rate.

^a Considered in many studies as reference standard, although this method frequently yields negative results in established ODRIs [78].

^b Single sample sent to laboratory for culture is rarely diagnostic; ≥3 specimens are considered appropriate.

^c Estimated LR; lack of unambiguous reference standard may overestimate LRs unless multiple biopsy samples are taken.

Table 5. Treatment options for patients with orthopedic device-related infection.

Option
Debridement with retention of prosthesis and long-term treatment with antimicrobial agents
Girdlestone arthroplasty
One-stage replacement with or without use of antimicrobial cement and long-term treatment with antimicrobial agents
Two-stage replacement with or without use of antimicrobial cement and long-term treatment with antimicrobial agents
Suppressive antimicrobial therapy
Arthrodesis
Amputation

0.05. The posttest probability that the patient has the disease is now <1%.

Such calculations quantify the clinical experience that presence of a normal ESR and CRP level basically rules out the presence of ODRI [50]. CRP levels are always elevated after surgery but should return to normal within 2–3 weeks [79]. Therefore, an elevated CRP level must be interpreted in the context of its natural course. Another example is the value of the intraoperative Gram's stain: A positive result (LR positive, 8.5) strongly supports the diagnosis of ODRI whereas a negative result (LR negative, 0.94) basically does not influence the pretest probability. Many authors in fact recommend abandoning this latter test [72]. In my opinion, a posttest probability of $\geq 95\%$ is sufficient for diagnosing and treating ODRI. However, specialized infectious diseases physicians and orthopedic surgeons with long-term experience are frequently necessary for optimal management of patients with ODRI.

A common workup for ODRI includes testing of WBCs and polymorphonuclear leukocytes, including a left shift, ESR and CRP determinations, plain radiographs, and aspiration arthrograms with several specimens for culture. Scintigraphy by means of a technetium (Tc^{99m}) scan, gallium citrate (Ga^{67}) scan, or indium (In^{111})-labeled leukocyte scan may be helpful in the diagnosis of ODRI. However, this approach is expensive, and the accuracy of these methods is still limited. They frequently fail, especially in equivocal situations in which standard radiographs are unable to distinguish between septic and aseptic loosening of the implant [38]. Intraoperative cultures should always be combined with histopathology (see below).

Standardized criteria for establishing the diagnosis of ODRI are lacking, and even though most studies use similar sets of criteria, they are not identical. The following are the criteria most studies use: (1) purulence surrounding the prosthesis at the time of debridement and isolation of the same pathogens in ≥ 2 specimens and a positive frozen section from a biopsy [42]; (2) systemic signs and symptoms of infection and pain at the site of the device without another obvious source, pu-

rent fluid in the joint or around a fixation device, and isolation of at least 1 pathogen from aspiration or intraoperative culture—the criteria for early, postoperative acute infection [11, 15]; (3) clinical signs and symptoms of ODRI with a positive culture result and positive results of histopathology; or (4) the presence of a sinus tract communicating with the prosthesis or internal fixation device, indicating chronic infection [50]. Some researchers use only microbiological criteria and define implant-associated infection by isolating a single pathogen from 3 different specimens [80]. Many other criteria are used but have not been validated and were applied on retrospective data.

MICROBIOLOGICAL CULTURES

The reference standard for diagnosing infection is the isolation of the responsible pathogen. However, standard microbiological cultures are only moderately sensitive and specific for diagnosing ODRI. A very low inoculum, adherent bacteria, and the formation of small-colony variants of *S. aureus* may limit detection. In addition, concurrent treatment with antimicrobial agents before sampling can prevent growth in the laboratory. Technical issues that can affect culture results include poor positioning of the aspiration needle or the addition of local anesthetic to the inflamed joint fluid.

Preoperative aspiration is probably the most useful tool to rule out the presence of ODRI or to confirm a clinically suspected ODRI [10]. The position of the needle should preferably be documented by arthrography or ultrasonography. The pathogen may be isolated from a synovial biopsy in cases of a dry tap. Three specimens should be sent to the laboratory for accurate interpretation of the results. The diagnosis of ODRI is established when all 3 specimens demonstrate growth of the same microorganism [80] and the patient has clinically suspected ODRI. Superficial sinus tract cultures are misleading, and only isolation of *S. aureus* may indicate the true infecting pathogen in osteomyelitis [81].

Intraoperative cultures provide the most accurate specimens for microbiological cultures and are frequently used as the reference standard for diagnosing ODRI. Simple technical problems, such as routine antimicrobial prophylaxis before sampling, delay in sending the specimens to the laboratory, failure to ask for anaerobe cultures, and sending in swabs instead of biopsy material, may limit the ability of the laboratory to isolate the microorganism. A minimum of 3 specimens should be sent to the laboratory [80]. The implant, if available, should be cultured as well [11, 45, 82]. Sonication may increase the sensitivity of the culture technique by dispersing adherent bacteria [82].

Molecular techniques are powerful tools that significantly enhance the detection of a microorganism. 16S rRNA gene amplification allows detection of any bacteria that do not grow

Table 6. Results of studies evaluating treatment of orthopedic device–related infections with device retention.

Pathogen	Treatment (dosage)	Duration	Unstable devices included	Cure as treated (%)	Reference
<i>Staphylococcus aureus</i> , coagulase-negative staphylococci	Ciprofloxacin (750 mg b.i.d.), rifampin (450 mg b.i.d.)	≥3 mo ^a	No	100	[11]
	Ciprofloxacin (750 mg b.i.d.), rifampin (450 mg b.i.d.)	≥30 mo	No	100	[15]
	Fusidic acid (500 mg b.i.d./t.i.d.), rifampin (450 mg b.i.d.)	≥6 mo	Yes	57	[14]
	Ofloxacin (200 mg t.i.d.), rifampin (450 mg b.i.d.)	≥6 mo	Yes	57	[14]
	Various	NS	Yes	31	[12]
	Various	>4 wk	No	71	[40]
Methicillin-resistant <i>S. aureus</i>	TMP-SMX (20/100 mg/kg)	>6 mo	Yes	43	[90]
<i>Pseudomonas aeruginosa</i>	Ceftazidime (1000 mg t.i.d.), ciprofloxacin (500 mg t.i.d.)	≥6 mo ^b	Yes	93	[91]

NOTE. In most studies, antimicrobial therapy was begun iv. mo, month; NS, not standardized; TMP-SMX, trimethoprim-sulfamethoxazole; wk, week.

^a Results from patients who completed trial are reported; cure rates from intent-to-treat analysis are slightly lower.

^b Ceftazidime for 6 weeks.

in routine culture or bacteria in a very low inoculum [45]. 16S rRNA–directed in situ hybridization may be less susceptible to cross-contamination [83]. These newer molecular techniques, however, do not provide susceptibility testing, a prerequisite for accurate treatment of ODRIs. In addition, they are not widely available, and identification of species requires bacterial sequencing or specific primers. As of today, more research is necessary to introduce such techniques in a routine microbiology laboratory for the identification of microorganisms in ODRIs.

HISTOPATHOLOGY

Any single high-power field that contains at least 5 stromal neutrophil granulocytes strongly suggests infection [84]. Frozen intraoperative sections correlate well with the permanent section of the capsular or granulation tissue [55]. Permanent sections improve sensitivity by ~10% compared with frozen sections, but the specificity is >95% with both methods [85]. Frozen sections facilitate or allow the diagnosis of ODRI and help to distinguish true infection from contamination (table 4). The accuracy of this technique depends on the experience and training of the histopathologist and the proper sampling of specimens from clinically inflamed tissue. Interobserver variability appears to be substantial, even in specialized institutions [10]. Moreover, sampling errors will lead to false-negative results. Interpretation of frozen sections from patients with rheumatoid arthritis and other nonbacterial joint infections is difficult. However, frozen sections are part of the most powerful tests in diagnosing ODRI (median LR positive, 20). The combination of 2 independent tests—histopathologic and microbiological—allows an accurate diagnosis and should be used as the current reference standard for diagnosing ODRI. The cutoff for a positive result is still a matter of debate. Lonner et al. [85] proposed the use of 10

instead of 5 polymorphonuclear leukocytes per high-power field (×400) to increase the specificity of the result to 99%. Unfortunately, the number of areas to be scanned in frozen sections is not standardized.

TREATMENT

Several options for treatment of ODRIs have been established (table 5) and depend on multiple factors such as type of infection (acute vs. chronic), the isolated pathogen and its susceptibility pattern, the fixation of the device, the quality and availability of the bone stock, and the training and experience of the orthopedic surgeon and the infectious diseases physician. Most authors recommend the removal of the device to eradicate chronic infection [2, 13, 86, 87]. Patients with chronic infections are not likely to respond to antimicrobial therapy alone and always require removal of the implant [2, 88]. A loose prosthesis cannot be successfully treated without removal of the implant [89]. However, many studies provide ample evidence that a subset of patients with acute ODRI can be successfully treated with retention of the device (tables 6 and 7). Criteria for optimal selection of patients for this type of treatment are summarized in table 2.

Early postoperative infection. Treatment of these early postoperative infections must be guided by an orthopedic surgeon and an infectious diseases physician trained in management of ODRIs [43]. Patients presenting with fever, redness, pain, and drainage early after surgery should never be treated with antimicrobial agents before a thorough diagnostic workup has been done. The preferred method, especially for patients with hematoma, is extensive and meticulous debridement that allows the taking of multiple biopsy samples from clinically infected tissue around the implant and multiple microbiological samples, including anaerobic cultures. Prophylactic antibiotics

should be withheld until the joint capsule has been incised and accurate specimens for histopathology and culture have been obtained [89]. This debridement must be done immediately after the onset of signs and symptoms of infection to prevent potential biofilm formation of the infecting pathogen and subsequent resistance to antimicrobial therapy [13, 21]. Preoperative aspiration may be an alternative, but cultures can be falsely negative.

Patients eligible for treatment with antimicrobial agents and salvage of the prosthesis or implant should meet all criteria listed in table 2. Initial treatment with antimicrobial agents should always be given iv. There is a current debate on how long treatment should be continued iv. The minimum duration supported by most authors is 2 weeks [11]. Tsukayama et al. [40] have recommended 4 weeks and other authors [2] 6 weeks. The treatment can be changed to oral therapy for a minimum of 3 months for internal fixation devices and hip prostheses and for 6 months for total knee prostheses [11, 15, 91, 93]. The isolated pathogen and its susceptibility pattern will guide the choice of antimicrobial therapy, on the basis of results of clinical studies (table 7). As mentioned above, the susceptibility pattern is useful only to exclude antimicrobial agents without in vitro efficacy. However, MICs demonstrate a poor correlation with clinical outcome. Serum bactericidal titers or MBCs with stationary-phase bacteria correlate much better with clinical outcome but are rarely available in the clinical setting [11, 15, 30]. The dosage of the treatment with antimicrobial agents should be as high as clinically possible. Ciprofloxacin failed to cure any tissue cages infected with *S. epidermidis* in the foreign body animal model, although trough levels of the antibiotic exceeded the MIC [30]. This failure correlated well with the poor in vitro efficacy against stationary-phase *S. epidermidis*. In contrast, ciprofloxacin was highly effective against stationary-phase *S. dublin*, and a case of ORDI with *Salmonella* was successfully treated with ciprofloxacin [17].

The BEC is usually 10–100 times higher than the regular MIC [34]. Rifampin has excellent efficacy against stationary-phase staphylococci, exceeds MICs at trough levels by a factor of 10–100, and is orally well absorbed. In addition, this drug has been shown to eliminate stationary-phase staphylococci in vitro, in an animal model with foreign body infections, and in clinical trials of ODRIs [11, 14, 15, 30]. Therefore, rifampin should always be included in the treatment of staphylococcal ODRIs if the strain is susceptible in vitro.

However, selection of resistant mutants occurs within days of rifampin monotherapy. Therefore, rifampin must be combined with another antimicrobial agent, preferably a quinolone. Quinolones effectively prevent the emergence of rifampin resistance if given concurrently. However, once resistance occurs, treatment should not be continued, even if the strain remains susceptible to quinolones. Data on treatment have been gen-

erated with such first-generation quinolones as ciprofloxacin or ofloxacin. The newer quinolones, such as moxifloxacin or gemifloxacin, have much lower MICs for staphylococci than the older quinolones and might be preferred as partner to rifampin. However, no clinical data are available.

The outcome of antimicrobial therapy appears to be associated with pharmacodynamic parameters. The optimal parameter of outcome for β -lactam antibiotics is probably the time above MIC [94]. Therefore, one should aim to exceed the MIC at trough levels for treatment with β -lactam antibiotics. The area under the inhibition curve (AUC) might be the best predictor for quinolone therapy [95]. The precise MIC should be determined for susceptible pathogens known to be close to the break point. Evidence for this hypothesis has been generated for *P. aeruginosa* and ciprofloxacin. Studies [96, 97] indicate a correlation between the AUC and the emergence of quinolone resistance. Therefore, combination therapy with a β -lactam antibiotic and tobramycin is recommended during iv therapy before switching to oral ciprofloxacin [91].

The patient should be closely monitored during treatment. Parameters to be recorded are clinical signs and symptoms of infection, WBC count, CRP level, ESR, and, less frequently, radiographic results. However, these parameters did not predict failure of treatment during the early course of therapy in a prospective study [11]. They are useful to identify failure of therapy, but a normal range of these parameters does not preclude relapse after withdrawal of antimicrobial therapy. Treatment should be continued for a minimum of 3 months for total hip prostheses and internal fixation devices or for 6 months for total knee prostheses. It should be continued for a maximum of 1 year if clinical or laboratory parameters have not normalized. Follow-up after completing antimicrobial therapy is crucial to identify failure of the treatment as early as possible.

Of importance, these recommendations apply only in the case of early postoperative infections that respond by >80% to this regimen. In my experience, longer intervals from surgery to the onset of infection (1–3 months) might be acceptable for pathogens with low virulence, such as CNS or *Propionibacterium* species [13]. However, failure rates are likely to be higher compared with immediate removal of the implant and treatment with antimicrobial agents.

Chronic infection. The diagnosis of chronic infection may be very difficult, because signs and symptoms may be absent. Aspiration with or without arthrography can help to distinguish infection from aseptic loosening of the implant. The presence of a sinus tract communicating with the prosthesis or internal fixation device implies definite chronic infection [50]. Treatment always calls for removal of the implant and a 1-stage or 2-stage revision arthroplasty.

Infections due to CNS are frequently treated with a 1-stage

Table 7. Antimicrobial therapy for acute orthopedic device-related infections.

Pathogen	Initial treatment (recommended dosage and route)	Duration of initial treatment (weeks)	Subsequent oral treatment (recommended dosage)
<i>Staphylococcus aureus</i> , coagulase-negative staphylococci (methicillin susceptible)	Nafcillin or flucloxacillin (not available in US; 2 g q.i.d. [8 g/day] iv) plus rifampin (450 mg b.i.d. orally) ^a	≥2	Ciprofloxacin (750 mg b.i.d.) plus rifampin (450 mg b.i.d.) ^a
<i>S. aureus</i> , coagulase-negative staphylococci (methicillin-resistant)	Vancomycin (1 g b.i.d. iv) plus rifampin (450 mg b.i.d. orally) ^a	4–6	High-dose cotrimoxazole (20/100 mg/kg/d) or high-dose quinolone (e.g., ciprofloxacin) (750 mg b.i.d.) or fusidic acid (500 mg t.i.d.) or vancomycin (1 g b.i.d. iv) or teicoplanin (400 mg/d iv or im) (not available in US) plus rifampin (450 mg b.i.d.) ^a
Streptococci	Penicillin (4 million U q4h iv) with or without gentamicin (1 mg/kg t.i.d. iv)	4–6 for penicillin, 2 for gentamicin	Amoxicillin (750–1000 mg t.i.d.) or ampicillin (500 mg q.i.d.)
Gram-negative bacilli (not <i>Pseudomonas aeruginosa</i>)	Quinolone (e.g., ciprofloxacin; 400 mg b.i.d. iv)	2	Quinolone (e.g., ciprofloxacin) (750 mg b.i.d.)
<i>P. aeruginosa</i>	Ceftazidime (2 g t.i.d. iv) or ceftepime (2 g t.i.d. iv) or meropenem (2 g t.i.d. iv) plus tobramycin (5 mg/kg/day iv)	4–6 for ceftazidime, ceftepime, or meropenem, 2 for tobramycin	Ciprofloxacin (750 mg b.i.d.)
Anaerobes	Clindamycin (600 mg t.i.d. iv)	2–4	Clindamycin (600 mg t.i.d.)

NOTE. Adapted from [92]. US, United States.

^a Patients >70 years old may not tolerate 450 mg of rifampin b.i.d. but may respond as well to lower dose of 300 mg b.i.d.

approach, if the quality of the bone stock is appropriate [98, 99]. Antibiotic-containing cement is commonly used but may be associated with subsequent aseptic loosening. Ure et al. [99] reviewed the failure rate after a 1-stage and a 2-stage approach and found no significant difference. However, infections due to low-virulence microorganisms are likely to be treated with a 1-stage approach, introducing a serious selection bias. Most orthopedic surgeons favor a 2-stage approach for frankly purulent infections due to a virulent pathogen, such as methicillin-resistant *S. aureus*. Such cases are treated by removing the implant, vigorous debridement, and 2–6 weeks of iv antimicrobial therapy before reinsertion of a new implant. Antimicrobial therapy may be discontinued before implantation of the new device to allow optimal conditions for intraoperative cultures. After the histopathologic specimens have been taken, antimicrobial prophylaxis should be infused before inserting the new implant.

Cultures may reveal additional pathogens or persistence of the isolated pathogens. Both results will influence treatment with antimicrobial agents and postoperative management. Negative culture results document successful treatment, allowing treatment with antimicrobial agents to be shortened after reimplantation. Antimicrobial prophylaxis should be given after biopsies and cultures to reduce the risk of reinfection of the new prosthesis. Such management may increase the risk for superficial surgical site infection but allow tailored treatment with antimicrobial agents. Surgical choice between a 1-stage or 2-stage approach and type and duration of antimicrobial therapy are poorly standardized and depend on the personal experience and local experts [38]. Other types of management, such as suppressive antimicrobial therapy, for patients not fit for surgery are beyond the scope of this review [100]. Excellent reviews of additional therapeutic options have been published elsewhere [2, 38, 89, 101].

In conclusion, treatment of ODRIs relies on an accurate classification, unambiguous diagnosis, and isolation of the infecting pathogen with its susceptibility pattern. Recent reports suggest that early postoperative infections can be successfully treated with debridement and long-term antimicrobial therapy. Patients must meet criteria such as a stable implant and good quality of bone stock; rapid treatment after onset of infection and orally available antimicrobial agents effective against the isolated pathogen are absolute requirements. In addition, the patient must be compliant and tolerate long-term antimicrobial therapy. This new option for a subset of patients will help to prevent the morbidity and mortality that were associated with the surgical 2-stage approach of treating ODRIs.

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