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Diagnosis and treatment of implant associated infections

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5.1 Introduction

Most implant infections, including artificial joint infections, are probably acquired in the operating theatre. Arguments to support this are the efficacy of perioperative antibiotic prophylaxis, and the similarity between skin flora and the pathogens that cause infections (Uçkay *et al.*, 2010b). Only a minority of infections are likely to be acquired in the first postoperative days (e.g. during dressing changes) or hematogenously from a distant focus. Overall, the lifetime infection rate is thought to be 0.5–2% for primary total joint arthroplasty, and 1–5% for fracture devices. Hematogenous infections contribute to roughly 20–25% of arthroplasty infections, and probably a much lower proportion of fracture-device infections (Osmon *et al.*, 2013; Uçkay *et al.*, 2009b). Typical hematogenous sources are skin, the urinary and the gastrointestinal tracts, endocarditis and pneumonia.

Although many different microorganisms can occasionally cause implant infection, the most prominent pathogens are Gram-positive bacteria originating from the human skin surface, in particular the staphylococcal species, which are evenly divided between coagulase-negative staphylococci and *S. aureus.* Streptococci also contribute to those infections (between 10% and 20% in different series), followed by other Gram-positive organisms ordinarily considered as 'contaminants' of cultures, such as *Corynebacteria* spp. *Propionibacteria* spp. and *Bacillus* spp. Gram-negative aerobic bacilli such as *Escherichia coli* or *Klebsiella* spp. have been identified in ≤25% of cases. Anaerobes such as *Peptostreptococcus* or *Bacteroides* spp. account for <5% of all episodes. Among arthroplasty patients with solid organ transplantations, e.g. kidney or liver transplants, atypical pathogens such as mycobacteria may occasionally be observed (Vergidis *et al.*, 2012). In roughly 10% of cases, no organisms can be detected.

Coagulase-negative staphylococci such as *S. epidermidis* frequently display multiple resistance determinants to many antibiotics (Raad *et al.*, 1998). Methicillin-resistant *S. epidermidis* (MRSE) is now commonly encountered in many healthcare institutions (Mohanty and Kay, 2004).

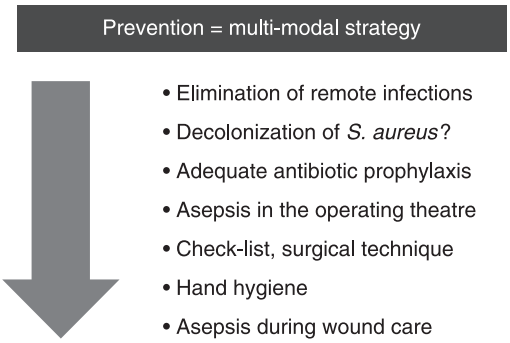
In addition, small-colony variants of *S. epidermidis*, a phenomenon well recognized in *S. aureus* (Vaudaux *et al.*, 2006), can emerge during glycopeptide therapy (Adler *et al.*, 2003). Small colony variants represent a subpopulation of bacteria which exhibit a slow growth rate, atypical colony morphology and unusual biochemical characteristics, thus making them a challenge for their identification by clinical microbiologists. The clinical consequences of this altered phenotype are the improved persistence of small colony variants in mammalian cells and their reduced susceptibility to antibiotics compared to their wild type counterparts, which make them nearly ideal candidates for recurrent infections (Proctor *et al.*, 2006).

However, microbiological summary would be incomplete if not to mention the biofilm. Biofilms are a matrix on the surface of infected implants consisted of proteins and other biological molecules. They are built by the host and the offending microorganism. Within this protective matrix, bacteria hide and are protected from host defences and antibiotic agents. Moreover, within biofilms, they usually survive in a dormant state. Because most antimicrobial agents kill during the replication phase, especially cell-wand acting drugs are inactive against dormant bacteria. It is estimated that up to 60% of microorganisms in nature live within a biofilm (Uçkay *et al.*, 2009c).

5.2 Risk factors and prevention

Prevention of surgical site infection (SSI) in orthopaedic surgery requires specific guidelines which are distinct from those applied for general surgery. This is explained by the low inocula that lead to implant- and biofilm-related foreign body infections, the pathogenic potential of skin commensals such as coagulase-negative staphylococci or propionibacteria, and a possible hematogenous origin for some infections. A prolonged post-discharge surveillance period with a minimal follow-up of one year is also required for implant-related surgery. The most frequently identified risk factors are diabetes mellitus, revision surgery, prolonged duration of surgery, advanced age, obesity, rheumatoid arthritis, as well as inappropriate antibiotic prophylaxis. Approximately half of all identified risk factors are endogenous and thus can hardly be modified during the immediate pre- and postoperative phase (Uçkay *et al.*, 2010b).

Furthermore, identifying a risk factor does not mean that its modification will automatically result in SSI reduction. At present, three to four preventive, high level (grade IA) evidence-based guidelines are proposed: surgical hand preparation (Widmer *et al.*, 2010); appropriate antibiotic prophylaxis (Prokuski, 2008, Uçkay *et al.*, 2010b); with some limitations, postponing an elective operation in the case of active remote infection; and preoperative decolonization of *S. aureus* skin carriage (Figure 5.1). Often these items are combined within intervention bundles targeting several single prevention measures at the same time (Uçkay *et al.*, 2010b)



5.1 Prevention of implant-related infections starts before elective surgery and continues life-long after implantation. Figure resuming key elements of prevention.

5.2.1 Perioperative antibiotic prophylaxis

Preoperative antibiotic agents are a key component of infection prophylaxis for most orthopaedic and traumatology interventions. In implant surgery, prophylaxis helps to reduce SSI rates from 4–8% without antibiotics to 1–3% according to trials performed in the 1970s and 1980s (Uçkay *et al.*, 2010b). Optimal timing of administration is of the utmost importance (Classen *et al.*, 1992), maybe even more important than adequate dosing. Several prospective and retrospective trials have demonstrated that the optimal window for the antibiotic being 'on board', i.e. the end of intravenous administration is situated between 30 to 15 minutes before incision. Earlier or later administration timing, e.g. two hours before or after, are associated with a doubled incision risk (Uçkay *et al.*, 2010b).

Despite the fact that infections due to methicillin-resistant *S. aureus* (MRSA) and MRSE are difficult to treat, the systematic use of vancomycin for antibiotic prophylaxis in those settings is not recommended. Many authors argue that with a high prevalence of methicillin-resistant clinical isolates in a given institution, vancomycin coverage might be justified. However, this logical assumption is not evidence-based on a routine basis. From an epidemiologic standpoint, there is no threshold for routine glycopeptide prophylaxis in settings where methicillin-resistant staphylococci are endemic. Furthermore, there is no evidence that a glycopeptide would be superior to cephalosporins for patients without MRSA carriage. A review of four randomized trials comparing the prophylactic use of teicoplanin vs. prophylactic cephalosporin in settings with a high prevalence of methicillin-resistance among *S. epidermidis* showed similar infection rates in both groups (Bolon *et al.*, 2004). The impact of internal colonization with extended-spectrum beta-lactamase (ESBL)-producing Gram-negative rods, vancomycin-resistant enterococci (VRE), or multiresistant non-fermenting rods (*P. aeruginosa*, *Acinetobacter* spp.), is less important for patients undergoing orthopaedic surgery compared to those with urologic or visceral surgery, because the hallmark of

orthopaedic infections are organisms that colonize the skin, and not the urinary or the intestinal tract (Agostinho *et al.*, 2013). As far as we know, there is no solid evidence for a change in routine antibiotic prophylaxis for orthopaedic surgery of patients colonized by those pathogens (Uçkay *et al.*, 2010b).

5.2.2 Antibiotic-containing cement for prophylactic purposes

Antibiotics can be added to bone cement and spacers, while prepackaged antibiotic-loaded cement is commercially available. The most extensive studies on prophylaxis with antibiotic-loaded cement in primary arthroplasty were performed in Scandinavia. Engesaeter and colleagues reviewed the revision rates for a total of 56000, either cemented or uncemented, primary total hip replacements (Engesaeter *et al.*, 2006). Prostheses implanted with antibiotic cement were associated with an overall lower life-time revision risk. The benefit of antibiotic-loaded cements was further confirmed in the Finnish arthroplasty register and in large meta-analyses (Jamsen *et al.*, 2009; Parvizi *et al.*, 2008), and by retrospective studies where cost-effective antibiotic cementing was shown to reduce SSI by up to 50% (Berbari *et al.*, 1998). A single prospective, randomized trial including 340 primary arthroplasties was performed, which compared a control group treated with plain cement with another group that received cefuroxime-impregnated cement. Both groups also received systemic antibiotic prophylaxis. The study showed a lower infection rate in the cefuroxime cement group (Chiu *et al.*, 2002). The same authors performed a similar prospective study with vancomycin-containing cement, but focusing on patients with revision knee arthroplasties.

5.2.3 Prophylaxis before dental interventions

The use of antibiotic prophylaxis for arthroplasty patients during dental or gingival interventions is still debated by orthopaedic surgeons, physicians and dentists, despite the fact that several opinion leaders, scientific reviews, official recommendations and cohort studies provide arguments against routine prophylaxis for these conditions. Infections of total hip or knee replacement due to hematogenous seeding following dental intervention are probably very rare, if they exist (Uçkay *et al.*, 2008). A good oral hygiene is the best prophylaxis and certainly more relevant than any topical or systemic antimicrobial use. As a rule, hematogenous infections are difficult to prevent. One way of preventing orthopaedic implant infection might be the rapid control of the remote source of established infection, which would be more efficient than a prophylactic approach.

5.2.4 Other measures with high efficacy

Systemic patient-related factors, such as malnutrition, diabetes mellitus, elevated serum glucose level, anticoagulation, smoking, or iatrogenic immune suppression

(steroid therapy or use of TNF-alpha inhibitors) play a role in wound healing and infection risk. The negative impact of some of these factors on SSI rates can be attenuated in the immediate pre- and postoperative period. For example, if possible, preoperative high-dose corticosteroid therapy should be tapered before elective orthopaedic surgery and glycaemia and anticoagulation optimized. Smoking cessation before and even after surgery is beneficial in terms of postsurgical complications leading to infection (Uçkay *et al.*, 2010b).

5.3 Diagnosis

Diagnosis of prosthesis infection can be difficult, in particular if there is no sinus tract communicating with the artificial joint or the presence of the same pathogen in at least two separate tissue or fluid samples from the affected joint. Diagnosis of infection frequently relies on a combination of clinical, anamnestic, laboratory and histological parameters (Parvizi *et al.*, 2011). There are no uniform clinical criteria for the diagnosis of implant infections. Most patients experience a long, indolent course of infection characterized by increasing joint pain and the occasional formation of cutaneous draining sinuses. A minority of patients have an acute fulminant illness associated with high fever, severe joint pain, local swelling, sinus track and erythema. Patients with late-onset infections due to hematogenous seeding can present with this acute onset of symptoms in one or several previously well-functioning joints. The pattern of clinical presentation is determined largely by the nature of the infecting microorganism (i.e., the symptoms are more prominent in *S. aureus* infections compared with *S. epidermidis*).

Persistent elevation of the erythrocyte sedimentation rate suggests infection, but is neither very sensitive nor very specific since it may be due to many other causes. The same is true for leucocytosis or C-reactive protein (CRP). The role of pro-calcitonin in non-bacteremic implant infections has to be further investigated. Several studies suggest that its values are elevated in nosocomial osteoarticular infections. However, most studies mix-up 'systemic', e.g. bacteremic infections, with localized osteoarticular infections without systemic signs of sepsis. For the latter, it is not sure that serum pro-calcitonin levels would also be pathological. Indeed, a study performed in our institution did not support the diagnostic or follow-up values of pro-calcitonin levels in localized othopaedic infections (Uçkay *et al.*, 2010a).

5.3.1 Radiology

A plain radiograph can display abnormal lucencies (>2 mm in width) at the bone–cement interface, changes in the position of prosthetic components, cement fractures, or the motion of components as a result of infection. . The sensitivity and the specificity of radiographic anomalies in diagnosing infection have been reported as 73% and 76%, respectively (Bernard *et al.*, 2004b). Magnetic resonance or computed tomography techniques for evaluating infection are of

little help, in particular because the presence of metal in prostheses interferes with these images. Scintigraphy demonstrates increased uptake in areas of bone with enhanced blood supply or increased metabolic activity (Smith *et al.*, 2001; Kraemer *et al.*, 1993). According to Bernard, sensitivity and specificity of bone scintigraphy is at best 76% (Bernard *et al.*, 2004b). Only limited data are available for positron emission tomography (PET).

5.3.2 Microbiological culture and histology

Several identical positive microbiological cultures identifying the same microorganisms are currently the gold standard to confirm the clinical suspicion of infection. As a result, the diagnosis of implant infection always requires obtaining microbiological samples of pus, synovia or tissue (Trampuz *et al.*, 2004). Alternatively, isolation can be achieved by blood cultures or sonication of explanted hardware (Trampuz *et al.*, 2007). Samples for mycobacterial and fungal cultures should be taken and processed if commonly cultured microorganisms are not present and if the clinical features are compatible. Often culture growth has to be monitored beyond the standard incubation period of five days, especially when suspecting propionibacteria (such as in the case of shoulder and spine implant infections). Cultures may be negative because of prior antimicrobial exposure, a low number of organisms, an inappropriate culture medium, fastidious organisms, or prolonged transport time to the microbiology laboratory. Some microorganisms, such as small colony variants are inherently difficult to detect. Eubacterial polymerase chain reaction (PCR) is usually less sensitive than microbial cultures and is still relatively expensive, which excludes its routine application. In polymicrobial colonization or infection, its interpretation can be difficult. Moreover, it does not provide information about antibiotic resistance, except for genes coding for methicillin-resistance. Nevertheless, specific or multiplex PCR is beneficial in special circumstances when very slow growing bacteria or those which are difficult to grow are suspected, such as *Kingella kingae, Brucella* spp., *Coxiella burnetii, Bartonella henselae,* or mycobacteria, including *Mycobacterium tuberculosis* and *M. ulcerans*. Tissue specimens should also be submitted for histopathologic study as special staining techniques may reflect unusual or slow-growing microorganisms. Histopathologic examination showing acute inflammation markers such as leucocytes has a $>80\%$ sensitivity and $>90\%$ specificity for the diagnosis of infection (Banit *et al.*, 2002). However, the results are dependent on appropriate sampling of the tissue harbouring the infection and the expertise of the pathologist.

5.4 Treatment

Treatment of orthopaedic implant infections is not standardized due to the variable clinical presentations and the lack of data from randomized, controlled trials. Treatment usually involves both medical and surgical measures (Zimmerli *et al.*,

2004), depending upon the cause and timing of the infection, and the condition of the host.

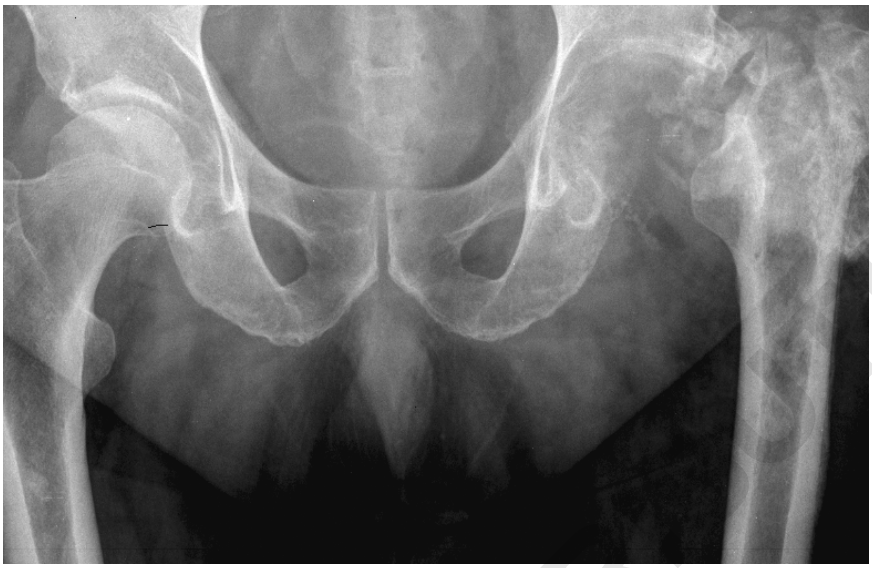
5.4.1 Surgical therapy

Antibiotic treatment alone, without surgical intervention involving at least a thorough debridement, is not considered standard and has been associated with high failure rates. Many surgeons would advocate a removal of the implant in any case that is feasible. However, in selected patients and mostly in fracture-device infections, debridement(s) with retention might be an option. This approach is limited to a small subset of patients, i.e., patients with an early (<4 weeks postoperatively) acute onset of symptoms and a well-fixed implant without signs of loosening or sinus tract. For some authors, infection with *S. aureus* is a relative contraindication to debridement and component retention (Uçkay *et al.*, 2009a), whereas others consider only the methicillin-resistant strains as a contraindication for prosthesis retention (Bradbury *et al.*, 2009).

5.4.2 Arthroplasty infections

When the diagnosis of arthroplasty infection is established, treatment options are debridement with prosthesis retention, resection arthroplasty, one- or two-stage reimplantation, or arthrodesis (Zimmerli *et al.*, 2004). Arthrodesis is a fusion of the adjacent bones over the (ancient) articulation. After arthrodesis, the articulation is stiff, and no more functional. The advantage is to have remission of infection, once the articular space does not exist anymore. Upon removal of the prosthesis and re-implantation, there are two options: one- or two-stage re-implantation of a new prosthesis. During the phase of no prosthesis (and no hip joint), the patient is left with a so-called 'Girdlestone' hip (Figure 5.2). There is no prospective randomized study with prolonged follow-up, which compared one-stage with two-stage arthroplasty (Zimmerli *et al.*, 2004; Winkler, 2009). In a two-stage procedure, the prosthesis is removed, followed by six weeks of antimicrobial therapy and two additional weeks of antibiotic-free window. If during the antibiotic-free window there is no clinical sign of recurrent infection, a new prosthesis is re-implanted roughly eight weeks after the explantation of the infected one. With one-stage exchange arthroplasty, the infected components are excised, surgical debridement is performed, and a new prosthesis is immediately put in place under antibiotic coverage. One-stage exchange arthroplasty may be suitable for highly selected hip prosthesis patients who have satisfactory soft tissue, no severe coexisting illnesses, no fistula, no need for bone graft, and who are infected with organisms that are highly susceptible to antimicrobial drugs (Winkler, 2009). Some authors have reported 85–90% success rates with this approach (Uçkay *et al*, 2009a; Winkler, 2009).

The two-stage approach requires careful surgical removal of all foreign body material and infected tissue followed by prolonged parenteral and oral therapy



5.2 Status after removal of total hip joint prosthesis (left; Girdlestone hip) due to chronic infection attributed to *Staphylococcus epidermidis*. (Property of Geneva University Hospitals; picture published with the permission of the patient).

(Zimmerli *et al.*, 2004, Bernard *et al.*, 2004a). Reported success rates of more than 90% can be achieved with two-stage replacement arthroplasty for infected hip prostheses with the interim use of antibiotic-loaded cement (Hsieh *et al.*, 2004). The advantages of two-stage re-implantation are that it allows for additional debridement and optimization of the total antibiotic consumption to a maximal duration of six weeks in the interval between the stages (Zimmerli *et al.*, 2004). The disadvantage is that the second intervention is more difficult because of scarring and can lead to a second perioperative morbidity and mortality risk for patients of advanced age and serious comorbidities. Of note, the precise duration of antibiotic therapy after debridement and implant retention is somewhat arbitrary with suggestions ranging from three to six months (for knee arthroplasties) (Zimmerli *et al.*, 2004; Laffer *et al.*, 2006). Joint aspiration prior to re-implantation is advocated by some experts to rule out dormant infection/presence of pathogens. This approach is not evidence-based in routine procedures and should be used in selected cases when the clinician is concerned about persistent infection. However, several studies revealed that the pre-implantational joint aspiration could provide false-negative or false-positive results regarding the presence of dormant bacteria (Schindler *et al.*, 2011). In contrast to frank infection, where bacteria are active and produce pus, joint aspiration might be insufficient to detect bacteria that decided to lurk in biofilms without active inflammation. Therefore,

the intraoperative samples upon re-implantation yield a better performance to detect these bacteria.

Antibiotic-impregnated spacers are used to maintain soft tissue tension around the joint during the interval between debridement and re-implantation in two-stage procedures. Arguments for this approach include high levels of local antibiotic delivery, improved exposure at the time of re-implantation, and the ability to maintain weight-bearing during the interval period (Uçkay *et al.*, 2009a). Nevertheless, no comparative trial has yet demonstrated that locally administered antibiotics were more effective than systemic antibiotics as well as a combination of local and systemic antibiotics, when considering recurrence rates of infection (Barth *et al.*, 2011).

5.4.3 Alternative approaches

Exchange surgery for arthoplasty infections is a fastidious, time-consuming, procedure and can be detrimental for patients with multiple comorbidities. An alternative option is a lifelong suppressive oral antimicrobial treatment without surgical intervention. Even in the context of a suppressive, palliative treatment, most experts recommend a lavage of the infected joint to reduce the inoculum size. Arthrodesis used for treatment of an infected arthroplasty can provide a stable, generally painless, limb with some expected shortening. The last option for the treatment of the infected arthroplasty is amputation. It essentially concerns infected knee arthroplasty. Amputation is indicated only for life-threatening infection or persistent local infection with massive bone loss.

5.4.4 Non-arthroplasty orthopaedic implant infections

There are many epidemiological data regarding the occurrence (roughly 1–5%) of orthopaedic fracture-device infections such as plates or nails for tibial or femur fractures. In contrast, surprisingly few data have been published regarding the management and outcome of their treatment. Experts' recommendations are analogous to those of other osteoarticular infections and include at least one surgical drainage, implant removal if feasible, associated with concomitant antibiotic prescription until osseous consolidation or during six weeks post removal, even though implant-associated infections are conceptually different from other orthopaedic infections. They usually lack the ongoing presence of an implant (usually removed, and which hampered infection cure) and they usually lack sequestrae, the hallmark of chronic osteomyelitis. In the literature (Uçkay *et al.*, 2009a, 2009c), the duration of antimicrobial administration concomitant to surgery, and variables associated with its failures, have so far been investigated for arthroplasty infections, less for chronic osteomyelitis cases, and even less so for implant-associated infection, the latter often with fewer than 30 episodes included per publication. Theoretically, complete implant removal is their most

essential part of treatment, and thus, a relatively short antibiotic administration could be enough for the sterilization of superficial bone layers adjacent to the implant.

5.4.5 Antibiotic treatment

Antibiotic therapy is very often concomitant to surgery and has some characteristics pertinent to osteoarticular and implant infections. One important issue is antimicrobial penetration into bone or bacterial biofilm. A review by Landersdorfer *et al.* (2009) on the penetration of antibacterials into bone emphasized the critical role of different assays for evaluating drug concentrations on the quality of the results. Steady-state bone levels of antibiotics in relation to their plasma levels after systemic administration may be influenced by several factors, including the physicochemical properties of the drug, its degree of protein binding and compartmental clearance, as well as by the particular structure of the bone tissue itself. For example, macrolides, linezolid and quinolones show mean bone-to-serum concentration ratios between 0.3 and 1.2, whereas the average ratios of bone-to-serum concentrations range from 0.15 to 0.3 for cephalosporins, penicillins and glycopeptides (Landersdorfer *et al.*, 2009).

Previously, experts usually recommended intravenous (IV) antibiotic therapy for 4–6 weeks (Uçkay *et al.*, 2009a) followed by an oral course of additional weeks or months. The rationale for a prolonged IV course was elevated serum concentrations. A more recent practice has been to switch from IV to oral therapy after an initial period of two weeks (Uçkay *et al.*, 2009a), although this mostly reflects expert opinion. Without doubt, bone penetration of antibiotic agents in parenteral administration is acceptable with a bioavailability in the blood per definition of 100% (Smilack *et al.*, 1976). At the same time, IV medication should be limited as far as possible to avoid unnecessary costs, prevent catheter-related complications, and to increase patient and nursing comfort. The estimated proportion of complications attributed to a prolonged IV course is approximately 15% (Matthews *et al.*, 2007). Recent retrospective data suggest that regimens with an early switch to oral antibiotics are as effective as prolonged parenteral regimens (Uçkay *et al.*, 2009a). As a clinical example, Cordero-Ampuero *et al.* (2009) cured 36 arthroplasty infections with oral antibiotics administered from the start.

Choice of antibiotics

Our personal antibiotic choices for the most commonly encountered microorganisms in infections of skeletal prostheses are presented in Table 5.1. Ideally, the agent should have bactericidal activity even against slow-growing and biofilm-producing bacteria. To some extent, rifampin fulfils these criteria for staphylococci. It can penetrate phagocytes and kill intracellular bacteria (Uçkay

Table 5.1 Antibiotic treatment of orthopaedic implant infections (in case of implant retention)

Microorganisms	Parenteral therapy	Equivalent alternatives	Oral therapy[a]
S. aureus or coagulase-negative			
Penicillin-sensitive	Penicillin G (4 million U 6x/d)	A cephalosporin II[b], clindamycin (600 mg 3x/d)	Amoxicillin (750 mg 3x/d)
Penicillin-resistant	Nafcillin[c] (2 g 4x/d)	A cephalosporin II[b], clindamycin (600 mg 3x/d)	Quinolone[d]-rifampin (600 mg 1x/d)
Methicillin-resistant	Vancomycin (2 x 15 mg/kg/d)	Teicoplanin[e] (400 mg 1x/d, 1st day 2x/d)	Fusidic acid-rifampin (1500 mg 3x/d, 600 mg 1x/d)
Various streptococci	Penicillin G (4 million U 6x/d)	Clindamycin (600 mg 3–4x/d)	Amoxicillin (750 mg 3x/d)
Enterobacteriacae	A cephalosporin III[f]	Cefepime (2 g 2x/d)	Quinolone[d]
P. aeruginosa	Piperacillin[g] (4 g 4x/d) and Gentamicin (5 mg/kg/day)	Quinolone (with aminoglycosides)	Quinolone[d]
Anaerobes	Clindamycin (600 mg 3x/d)	Amoxicillin-clavulanic acid (1.2–2.2 g 3x/d) or metronidazole for Gram-negative anaerobes (500 mg 3x/d)	Clindamycin (600 mg 3x/d)
Mixed infection	Amoxicillin-clavulanic acid (1.2–2.2 g 3x/d)	Imipenem[h] (500–1000 mg 4x/d)	Amoxicillin-clavulanic acid (1000 mg 3x/d)

Notes

[a] Oral therapy is usually given after 1–2 weeks of parenteral therapy (with the exception of quinolones or clindamycin orally sooner).
[b] Second generation, such as cefuroxime (1500 mg 3x/d).
[c] Flucloxacillin in Europe.
[d] Quinolone, such as ofloxacin (200 mg 3x/d), ciprofloxacin (500–750 mg 2x/d), or fleroxacin (400 mg 1x/d).
[e] Teicoplanin is presently available only in Europe; it may be given by the intramuscular route.
[f] Third generation, such as ceftazidime (2 g 3x/d).
[g] Depends on sensitivities; piperacillin/tazobactam and imipenem are useful alternatives.
[h] In cases of gram-negative microorganisms resistant to amoxicillin-clavulanic acid.

Source: Adapted from Uçkay I. *et al.* (2009a).

et al., 2009a), but may lead to the rapid emergence of rifampin-resistant staphylococci during monotherapy. Hence, rifampin should always be used in combination (Zimmerli *et al.*, 1998; Uçkay *et al.*, 2009a). The dose of rifampin in combination therapy is also a matter of debate. In contrast to rodents in which higher doses led to better cure rates, no prospective randomized trials exist in humans. Doses of 1×600 mg, 2×450 mg, or 2×600 mg are used in routine practice. The authors of this chapter prefer 600 mg once daily. A panel of different antibiotics has been used in combination with rifampin, such as co-trimoxazole, fusidic acid, tigecycline, daptomycin, linezolid, dalbavancin, quinupristin/dalfopristin, minocycline, ofloxacin, ciprofloxacin and levofloxin (Uçkay *et al.*, 2009a). When prescribing rifampin, physicians have to remember potential interactions with other medications, such as warfarin, antiepileptic drugs, anti-HIV treatment, contraceptives, or steroids. Rifampin can colour body liquids in orange or red and can provoke nausea and hepatitis.

Beta-lactam antibiotics can be used for as long as the pathogen is susceptible. As a group, this large class of antibiotics has one important drawback, i.e., the low oral bioavailability together with a low intraosseous and synovial penetration (Uçkay *et al.*, 2009a). Vancomycin is a glycopeptide that inhibits cell-wall synthesis and has a serum half-life of 6 hours. Minimal serum trough levels of 20 mg/ml are believed to be optimal for treating bone infections (Hidayat *et al.*, 2006). Often, nephrotoxicity concerns argue against such a high dose. This issue has been exaggerated in the past, and often confounded with the use of concomitant nephrotoxic agents, in particular aminoglycosides. In continuous perfusion, the changes in vancomycin plasma levels are much lower than in intermittent application. The target concentrations are achieved faster with less adverse drug effects (Boffi El Amari *et al.*, 2004). However, continuous perfusion does not guarantee a better outcome in terms of remission. Teicoplanin is available in Europe and elsewhere, but not in the USA. It is a glycopeptide with a long serum half-life of 72 hours (LeFrock *et al.*, 1992), which is parentally administered within 30 min, generally at a dose of 400 mg once a day (after a loading dose of 2×400 mg the first day). Alternatively, teicoplanin can be given intramuscularly or three times a week (LeFrock *et al.*, 1992). Daptomycin depolarizes membranes and yields a rapid, dose-dependent bactericidal effect. It is only available in parenteral form and administered once a day at a dose of 6–8 mg/kg in the absence of renal dysfunction, which makes it suitable for outpatient treatment. The efficacy of daptomycin has been assessed by clinical trials for treating osteoarticular, skin and soft tissue infections (Jugun *et al.*, 2013).

Tigecycline belongs to the glycylcyclines, a further development of tetracycline antibiotics with a five times higher affinity to the target. It inhibits ribosomal protein synthesis and is only available in parenteral form: a charging dose of 100 mg, followed by 50 mg twice daily (IV). Today, ithas to be considered as an experimental drug for osteoarticular infections (Ellis-Grosse *et al.*, 2005). Aminoglycosides are not indicated for implant infections. They are less active in

synovial fluid or in bone (Uçkay *et al.*, 2009a) and their activity is substantially reduced in a low pH and low oxygen environment (Barth *et al.*, 2011). Furthermore, staphylococcal SCVs, a hallmark of chronic pre-treated osteoarticular *S. aureus* infections, are generally resistant to aminoglycosides (Uçkay *et al.*, 2009a). Linezolid inhibits ribosomal protein synthesis and can be administered parenterally or orally at a dose of 600 mg twice daily without adjustment for renal insufficiency. It is bacteriostatic with no cross-resistance to other antibiotics and is essentially anti-Gram-positive. Due to its excellent bioavailability of 100%, tigecycline is a good choice for outpatient treatment (Uçkay *et al.*, 2009a). Nevertheless, it also features some inconveniences. Apart from its high cost, it is associated with reversible bone marrow suppression, particularly thrombopenia, during administration of more than two weeks. Regular control of the hematogram is mandatory. Optic neuropathy and non-reversible peripheral neuropathy have been reported in 2–4% (Bishop *et al.*, 2006) of patients with prolonged administration. A severe serotonin syndrome in co-medication with certain antidepressant drugs, such as monoamine oxidase inhibitors, has been described (Bernard *et al.*, 2003).

Co-trimoxazole is an inexpensive bactericidal folate antagonist. Clinical experience shows that this molecule can heal small soft tissue infections (Markowitz *et al.*, 1992). One reason for failure in severe infections might be the amount of thymidine released from damaged host tissues and bacteria, a concept strengthened by the fact that *S. aureus* thermonuclease releases thymidine from DNA. Thymidine antagonizes the anti-staphylococcal effects of both trimethoprim and sulfamethoxazole, the two components of co-trimoxazole. Thus, failure with co-trimoxazole may well depend on the amount of tissue damage and organism burden (Markowitz *et al.*, 1992). Main adverse events during prolonged medication are nausea, rash, myelosuppression, allergy and hepatitis. Tetracyclines (doxycycline and minocycline; both 100 mg twice daily) are lipophilic, facilitating the passage into tissues. They are often combined with rifampin, although firm data are lacking.

Oral fusidic acid administered 500 mg three times daily has demonstrated efficacy in osteo-articular infections (Drancourt *et al.*, 1997) and inhibits protein synthesis. Most experts do not recommend monotherapy because of the development of (potentially reversible) resistance (Turnidge and Collignon, 1999). The antibiotic can be combined with rifampin. Hepatic failure has been reported with the use of fusidic acid and rifampin combinations and thus monitoring of liver function is advisable. Streptogramins such as quinupristin-dalfopristin (IV) or pristinamycin (oral) inhibit protein synthesis by binding to bacterial ribosomes. Quinupristin-dalfopristin administration requires central venous access and dextrose infusion. However, adverse effects, such as myalgias, arthralgias and nausea limit its use (Uçkay *et al.*, 2009a).

For anaerobic, streptococcal and staphylococcal osteomyelitis, bacterial protein synthesis inhibition by clindamycin 600–900 mg three times daily may be an option. The efficacy of clindamycin in bone infection can be explained by its excellent

penetration despite its classification as a bacteriostatic agent (Czekaj *et al.*, 2011). But there is a potential pitfall. For isolates routinely tested as susceptible for clindamycin, but resistant to erythromycin, clindamycin resistance may be inducible during ongoing treatment (Yilmaz *et al.*, 2007). Although staphylococci may be susceptible to fosfomycin and chloramphenicol, these antibiotics have not been much approved for osteoarticular infections (Falagas *et al.*, 2008) and should be avoided. For anaerobic osteomyelitis, metronidazole is the drug of choice (Uçkay *et al.*, 2009a), as are quinolones (Lew and Waldvogel, 1999) for Gram-negative infection. Quinolones are the only available class for Gram-negative infections in oral form and are therefore precious. *Pseudomonas aeruginosa* and other non-fermenting Gram-negative rods may rapidly develop resistance in monotherapy. Therefore, a combination with another parenteral drug or prolonged IV treatment in pseudomonal osteomyelitis would be wise. However, to the best of our knowledge, no antibiotic treatment adapted to this situation has been studied so far.

Duration of antibiotic therapy

For arthroplasty-associated osteomyelitis, antibiotics are initially administered IV for two weeks and followed by an oral therapy for a total treatment duration of three months in patients with retained hip prostheses, and three to six months in those with retained knee prostheses (Uçkay *et al.*, 2009a), although this arbitrary duration might be excessive (Puhto *et al.*, 2012). In the case of prosthesis removal, a six-week course of total antibiotic therapy is considered sufficient (Bernard *et al.*, 2010, Zimmerli *et al.*, 2004). The arbitrary limits of 6, 12, or 24 weeks is uniquely based on expert opinion rather than on prospective trials. After this long treatment, antibiotics can be stopped, regardless of actual CRP values or other inflammatory parameters (Piso and Elke, 2010). Indeed, personal experience combined with literature reports suggest that stopping antibiotics, even in the presence of elevated CRP, does not alter recurrence risk, which ranges between 10–25% depending on patient co-morbidities, pathogens, and the completeness of surgical debridement.

Interestingly, in general practice, the duration of antibiotic administration does not depend on the pathogen with a few exceptions, i.e., those proven to require long-lasting antibiotic treatment for eradication, such as tuberculosis and other mycobacteria, fungi or Q fever. This standard duration of concomitant antimicrobial treatment has been maintained for three decades, although there are some hints that antibiotic-resistant pathogens, especially *P. aeruginosa* (Seghrouchni *et al.*, 2012) or MRSA (Teterycz *et al.*, 2010; Treacy and Hyde, 2003), might be associated with higher treatment failures.

5.5 Future aspects

Improved knowledge of metabolic properties of biofilm-grown bacteria is still needed (Uçkay *et al.*, 2009c). Innovative approaches such as bacteriophages may

prove to be superior to established combined antibiotic therapies. Finally, it is very difficult to evaluate implant-related infections in small clinical studies or single centres. Hopefully, the future will show prospective and multicentre human cohort studies.

5.6 References

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