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Antimicrobial Agents in Orthopaedic Surgery

Prophylaxis and Treatment

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Abstract

The pathogenesis of implant-associated infection involves interaction between the microorganisms (biofilm formation), the implant and the host. Despite improvement of perioperative prophylaxis, orthopaedic implants still remain highly susceptible to bacterial or fungal contamination, generally resulting in persistent implant-associated infection. Therefore, perioperative and life-long prevention of infection is important. For perioperative prophylaxis, a first- or second-generation cephalosporin is recommended, which should be administered between 60 and 30 minutes before incision. The duration of prophylaxis should

not exceed 1 day. In centres with a low incidence of infection, a single dose is sufficient. Treatment of infections associated with orthopaedic devices usually requires appropriate surgical intervention combined with prolonged antimicrobial therapy. The choice of the antimicrobial regimen depends on the duration and pathogenesis of infection, stability of the implant, antimicrobial susceptibility of the pathogen and condition of the surrounding soft tissue. The role of rifampicin (rifampin), which has excellent activity on adherent staphylococci, in combination with β-lactams, glycopeptides, fluoroquinolones, minocycline, cotrimoxazole or fusidic acid, in the treatment of staphylococcal infections is outlined. Increasing antimicrobial resistance requires the use of alternative agents, such as quinupristin/dalfopristin, linezolid and daptomycin, but results of clinical trials with these agents are limited. Also reviewed are potential new antimicrobial agents currently undergoing investigation, such as the novel oxazolidinone RWJ-416457, the new glycopeptide dalbavancin, the glycylcycline compound tigecycline, the new carbacephem BP-102 and novel rifamycin derivatives. Vaccination against *Staphylococcus aureus* with StaphVAX® induced specific antibodies potentially preventing bacteraemia; however, there are no studies on efficacy in the prophylaxis of device-associated infections with this vaccine.

The number of trauma and aged patients requiring internal fixation devices or joint replacement is steadily increasing. In the US, about 2 million fracture-fixation devices are inserted annually.[1] Despite considerable progress in prevention and treatment of prosthetic joint-associated infection, the absolute number of patients with such infections has increased, as a result of the lifelong risk for bacterial seeding on the implant.[2] In patients with primary hip replacement, the infection rate during the first 2 years is usually <1%, and in those with knee replacement <2%. On average, about 5% of initially inserted internal fixation devices become infected, and the average cost of combined medical and surgical treatment is estimated to be $US15 000.[1] The incidence of infection after internal fixation of closed fractures is generally lower (0.5–2%), whereas the incidence may exceed 30% after fixation of open fractures.[3-6] The use of antimicrobial prophylaxis or pre-emptive therapy in patients with grade III open fractures has substantially decreased the frequency of implant-associated orthopaedic infections.[7] Since haematogenous infections occur at any time after surgery, the actual incidence per device-life is unknown. The reported infection rate is underestimated, since the follow-up in most published series is limited, and since many cases of presumed aseptic failure may be due to infection.

Well designed studies comparing different surgical and antibacterial treatment options are lacking. Therefore, treatment of implant-associated infections is mainly based on tradition, personal experience and liability aspects, resulting in substantial difference of treatment concepts between institutions and countries. In this review, the pathogenesis, prophylaxis and treatment of orthopaedic device-associated infection is discussed.

1. Pathogenesis

1.1 Interaction between Microorganisms, Implant and Host

Orthopaedic device-associated infections are traditionally difficult to treat. Foreign bodies remain devoid of a microcirculation, which is crucial for host defence and the delivery of antibacterials. Classically, all hardware has been removed in order to completely eliminate infection.[8] New data from *in vitro* studies, animal experiments and clinical trials has challenged this dogma.[2] In order to understand the novel concepts in antimicrobial therapy, the pathogenesis, which defines the treatment requirements, must be known.

The pathogenesis of implant-associated infection involves interaction between the microorganisms, the implant and the host. Adherence of *Staphylococ-*

cus epidermidis to the surface of the device involves rapid attachment to the surface of the implant mediated by nonspecific factors (such as surface tension, hydrophobicity and electrostatic forces), or by specific adhesions. This initial phase of adherence is followed by an accumulative phase during which *S. epidermidis* bacterial cells adhere to each other and form a biofilm, a process that is mediated by the polysaccharide intercellular adhesin encoded by the *ica* operon.[9] Adherence of *S. aureus* is more dependent on the presence of host-tissue ligands, such as fibronectin, fibrinogen and collagen.

Implant-associated infections are typically caused by microorganisms growing in biofilms.[10] These microorganisms live clustered together in a highly hydrated extracellular matrix attached to a surface.[11] Depletion of metabolic substances and/or waste product accumulation in biofilms causes microbes to enter into a slow- or non-growing (stationary) state, rendering them up to 1000 times more resistant to most antimicrobial agents than their planktonic (free-living) counterparts.[12,13] The presence of a foreign body significantly increases the susceptibility for infection.[14]

1.2 Routes of Infection

Implant-associated infections occur either by direct inoculation into the surgical wound during surgery or immediately thereafter during the first postoperative days (perioperative infection), by microbial spread through blood from a distant focus of infection (haematogenous infection), by direct or lymphogenic spreading from an adjacent infectious focus, or as a result of penetrating trauma (contiguous infection). Table I shows the classification of implant-associated infections according to the onset of symptoms after implantation.

1.2.1 Prosthetic Joint Infections

'Early infection' is defined as appearance of the first signs and symptoms of infection during the first 3 months after surgery at the implant site. This type of infection occurs by the exogenous route and is generally caused by highly virulent microorganisms (e.g. *S. aureus*). 'Delayed (low-grade) infection' is defined as appearance of the first manifestation of infection 3–24 months after surgery. In most of these cases, microorganisms of low virulence (e.g. coagulase-negative staphylococci, *Propionibacterium acnes*) are inoculated during surgery. 'Late infection' is defined as the appearance of the first signs and symptoms of infection >2 years after surgery. At this time, most infections result from haematogenous seeding.

1.2.2 Infections Associated with Internal Fixation Devices

These infections are classified as 'early' (<2 weeks), 'delayed' (2–10 weeks) and 'late' (>10 weeks).[15] Infections with delayed and late manifestations are usually referred to together, since their clinical presentation, treatment and prognosis are similar.[16] These infections generally occur exogenously, either by the penetrating trauma itself, during insertion of the fixation device or during disturbed wound healing.[17-19] Haematogenous infection is less frequent and is mainly caused by bacteraemia originating from skin, respiratory, dental and urinary tract infections.[20,21] Similar to prosthetic joint infections, early infections are caused mainly by highly virulent organisms such as *S.*

Table I. Classification of implant-associated infections according to the onset of symptoms after implantation

Classification	Onset of infection after implantation		Pathogenesis	Typical microorganisms
	prosthetic joint infections	infections associated with fracture fixation devices		
Early infection	<3mo	<2wk	During implant surgery or the following 2–4d	Highly virulent organisms such as *Staphylococcus aureus* or Gram-negative bacilli
Delayed infection	3–24mo	2–10wk	During implant surgery with delayed manifestation	Less virulent organisms such as coagulase-negative staphylococci or *Propionibacterium acnes*
Late infection	>24mo	>10wk	Predominantly caused by haematogenous seeding from remote infections	Typically caused by virulent microorganisms such as *S. aureus,* β-haemolytic streptococci or Gram-negative bacilli

aureus or Gram-negative bacilli, whereas delayed and late infections are caused mainly by microorganisms of low virulence (e.g. coagulase-negative staphylococci).

1.3 Diagnosis of Infection

No single routinely used test achieves sufficient accuracy for the diagnosis of infection. Therefore, a combination of clinical, laboratory, histopathology, microbiology and imaging studies is usually required. Preoperative aspirate of fluid accumulation and intraoperative tissue cultures provide the most accurate specimens for detecting the infecting microorganism. Paired samples, for microbiology and histopathology, should be taken from at least three intraoperative tissue areas. The degree of infiltration with acute inflammatory cells may vary considerably between specimens from the same patient. It is important to discontinue any antimicrobial therapy at least 2 weeks before tissue sampling for culture, if possible.[22] Perioperative prophylaxis at revision surgery should not be started until after tissue specimens have been collected for culture.[23] If the implanted material is removed, it can be cultured in enrichment broth media. The most common microorganisms causing implant-associated infections are shown in table II. *S. aureus* and coagulase-negative staphylococci are the most frequent infective agents, followed by streptococci, Gram-negative bacilli, enterococci and anaerobes.[24-26]

Table II. Distribution of microorganisms causing implant-associated infections. Data are compiled from 40 episodes of infections associated with total knee arthroplasty[24] and 63 episodes with total hip arthroplasty[25]

Microorganism	Frequency (%)
Staphylococcus aureus	33–43
Coagulase-negative staphylococci	17–21
Streptococci	11–12
Gram-negative bacilli	5–14
Enterococci	3–7
Anaerobes	2–5
Polymicrobial	5–13
Unknown	5–6

2. Prophylaxis

2.1 Nasal Decolonisation of *Staphylococcus aureus* Carriers

S. aureus is the most important microorganism causing prosthetic joint-associated infection.[21,24] In a recent prospective study, 14 of 1278 *S. aureus* nasal carriers (1.1%) had a bacteraemia with the identical strain at a later timepoint.[27] Thus, nasal decolonisation with mupirocin may be a rational strategy to reduce the risk of haematogenous implant-associated infection. However, the benefit of decolonisation with mupirocin prior to orthopaedic surgery has never been proven. In a double-blind, randomised, placebo-controlled study with 614 patients assessed after implantation of an orthopaedic device, surgical site infection due to *S. aureus* occurred in 1.6% of the patients in the mupirocin group versus 2.7% of those in the placebo group (relative risk [RR] 0.59, 95% CI 0.20, 1.79).[28] Similarly, in another large controlled trial, in which 891 patients were randomised to mupirocin or placebo before general, gynaecological, neurological or cardiothoracic surgery, the frequency of surgical site infection was similar in both groups.[29] Therefore, mupirocin prophylaxis cannot be generally recommended in patients prior to orthopaedic implant surgery. Nevertheless, mupirocin nasal ointment should be considered in patients colonised with methicillin-resistant *S. aureus* (MRSA) who undergo non-emergency orthopaedic procedures. In addition, such patients should be strictly isolated in the hospital and their intervention should be planned as the last of the day.

2.2 Perioperative Antibacterial Prophylaxis

2.2.1 General Principles

The role of foreign material in potentiating wound infection was first reported by Elek and Conen,[30] who demonstrated a 10 000-fold increased risk for skin abscesses in the presence of suture material in human volunteers. We confirmed the increased susceptibility to infection by the presence of foreign material in a guinea-pig infection model.[14] A locally acquired granulocyte defect induced by continuous activation of granulocytes by

the non-phagocytosable implant was found to be a crucial pathogenetic mechanism.[14,31] Since <100 colony-forming units (cfu) of *S. aureus* may cause persistent implant-associated infection, surgical site infections occur despite correct aseptic surgical practice. Antibacterial prophylaxis is indicated mainly in procedures associated with a high risk of infection, such as clean-contaminated or contaminated operations.[32] Among 47 000 clean-surgery procedures, the incidence of infection was 1.5%.[33] In these procedures, antibacterial prophylaxis is generally not indicated because it is not cost efficient. However, since each device-associated infection has devastating consequences for the patient and their surgeon, perioperative prophylaxis has become standard practice in all surgeries using implants.[34]

Prophylaxis of surgical site infection depends not only on appropriate antibacterial prophylaxis, but also on aseptic surgical management, proper awareness and avoidance of modifiable risk factors. The quality standard for antimicrobial prophylaxis in surgical procedures has been published by an expert group from the US, recommending intravenous antimicrobial prophylaxis in orthopaedic procedures with hardware insertion.[35]

The risk of infection varies according to the type of fracture and the surgical procedure. Patients undergoing joint replacement or fixation of closed fractures have a frequency of infections of 0–5%. Patients with fixation of open fractures have infection frequencies between 5% (grade I) and >50% (grade III A–C).[36] Since in grade III open fractures extensive soft-tissue damage occurs, surgery takes place in a heavily contaminated site. Therefore, short-term pre-emptive treatment of 5–10 days should be administered rather than prophylaxis.

2.2.2 Selection of Appropriate Antibacterial Prophylaxis

Various antibacterial agents have been successfully evaluated in perioperative prophylaxis. The drug should be active against the most common pathogens involved in implant-associated bone infection, namely staphylococci, streptococci and Gram-negative bacilli (table II).[24,25,37] The susceptibility of these microorganisms may differ considerably. Therefore, each hospital needs to continuously update the resistance pattern of their own surgical site isolates. In addition, the risk of toxic and allergic reactions to the prophylactic antibacterial should be as low as possible. Antibacterial agents with a high potency to select resistant strains, such as cefoxitin or ceftazidime, which are strong inducers of β-lactamases, should be avoided. In comparable substances, antibacterial cost may further guide the choice of the prophylactic agents.

In bone surgery, a first- or second-generation cephalosporin, such as cefazolin, cefamandole or cefuroxime is a rational choice. If the patient is allergic to cephalosporins, or in settings with high prevalence of MRSA, vancomycin or teicoplanin are alternative options. In contrast, vancomycin or teicoplanin should not be used in centres with high prevalence of methicillin-resistant coagulase-negative staphylococci. This recommendation is based on two arguments. First, cefamandole may be prophylactically active against methicillin-resistant coagulase-negative staphylococci.[38] Secondly, the US Centres for Diseases Control and Prevention (CDC) discourage the use of glycopeptides for routine surgical prophylaxis, in order to prevent the spread of vancomycin resistance.[39] Even in countries with a high prevalence of MRSA, no evidence of superiority of a glycopeptide prophylaxis exists. For example, in an Italian study comparing a single dose of teicoplanin with two doses of cefamandole, both prophylactic regimens were equally efficient in 496 patients undergoing total hip replacement.[40]

2.2.3 Timing of Prophylaxis

For optimal efficacy of the prophylactic agent, antibacterial inhibitory concentrations must be achieved in tissue at the time of incision and last during the entire procedure. In the pioneer animal study of Burke,[41] a short period of prophylactic efficacy of 3 hours has been observed. By delaying the antibacterial administration to 4 hours after subcutaneous bacterial inoculation, the effect of prophylaxis was completely abolished. These animal data have been confirmed with a large retrospective clinical study evaluating outcome of 2847 surgical wounds.[42] In this study, the risk of surgical site infection increased 6-fold when prophylaxis was given either too early (>2 hours before surgery) or too late (>3 hours after surgery). On the basis of these studies, perioperative prophylaxis should be

administered intravenously 60 minutes before incision.[36] According to a recent study, in which only one or two doses of intravenous cefuroxime were given for prophylaxis, the incidence of surgical site infection in 4557 patients was 1.3% when the drug was given between 60 and 30 minutes before incision, compared with 4–6% ($p < 0.0001$) when it was administered earlier or later.[43] Thus, antibacterial prophylaxis should be given not earlier than 1 hour and not later than 30 minutes before incision.

In one study, when a tourniquet was used, tissue concentrations of the antibacterial were insufficient to prevent surgical site infection when administered 5 minutes before inflation or later.[44] In another study, the time interval was 10 minutes and longer.[45] Therefore, antibacterial prophylaxis should be administered at least 10 minutes before inflation of the tourniquet.

2.2.4 Review of Controlled Studies of Prophylaxis in Fracture and Orthopaedic Surgery

There are only a few placebo-controlled studies dealing with antibacterial prophylaxis of device-associated infections. Many studies have been ended prematurely because of devastating consequences of these infections. Nevertheless, the available information allows evaluation of the role of antibacterial prophylaxis in fracture and orthopaedic surgery, including five placebo-controlled studies with a total of 4728 patients (table III).[46-50] In four of the five studies, the incidence of infection was significantly lower in patients receiving antibacterial prophylaxis than in the placebo group, regardless whether an arthroplasty or an internal fixation was performed (incidence of infection 0.9–3.6% with antibacterial prophylaxis versus 3.3–8.3% with placebo). The only study not demonstrating significant differences was probably underpowered.[49] In a recent meta-analysis, data from 8307 patients with surgery for closed fractures of long bones included in 22 randomised controlled trials showed a decrease of deep wound and other infections in the group with single- or multiple-dose antibacterial prophylaxis (RR 0.40, 95% CI 0.24, 0.67).[51] Thus, antibacterial prophylaxis is clearly indicated in fracture and orthopaedic surgery.

In these studies, different regimens were used in the active arm, from first- to third-generation cephalosporins, and from single-dose to 5-day prophylaxis. Further studies were performed, comparing different antibacterials or different treatment durations. Table IV summarises five controlled studies with a total of 4918 patients comparing a short- versus a long-duration regimen.[52-56] Prophylaxis of >1 day was not superior to the short course. However, in the study of Gatell et al.[53] a 1-day course of cefamandole resulted in a significantly lower infection rate than a single dose. In another study, with cefuroxime, the 1-day prophylaxis resulted in a 1.8-fold reduction of joint infection compared with a single dose in a total of 2651 patients.[54] Despite the large sample size, this difference was not significant ($p = 0.17$), probably due to the low infection frequency in both groups. Thus, the duration of prophylaxis should not exceed 1 day, and 1-day prophylaxis should be preferred to a single dose in centres with a high incidence of infection.

In patients with open fractures, only a few controlled studies have been performed, using pre-emptive therapy, not prophylaxis.[57-59] Open wounds with heavy microbial contamination were treated for 10 days. In the study of Patzakis et al.,[57] the incidence of infection after fixation of open fractures was 11 of 79 (14%) in the control arm, 9 of 91 (10%) in the penicillin/streptomycin arm, and 2 of 84 (2%)

Table III. Prospective, placebo-controlled trials of antibacterial prophylaxis in bone surgery

Study (year)	Surgical procedure	Rate of infection		p-Value
		placebo	active drug (duration)	
Hill et al.[46] (1981)	Hip replacement	35/1067 (3.3%)	Cefazolin (5 days) 10/1070 (0.9%)	0.001
Gatell et al.[47] (1984)	Different fixation devices	11/150 (7.3%)	Cefamandole (1 day) 2/134 (1.5%)	<0.05
Bodoky et al.[48] (1993)	Dynamic hip screw	6/115 (5%)	Cefotiam (1 day) 1/124 (1%)	<0.05
Paiement et al.[49] (1994)	Internal fixation of ankle fracture (with tourniquet)	3/62 (4.8%)	Cefalotin (1 day) 1/60 (1.7%)	NS (0.33)
Boxma et al.[50] (1996)	Various internal fixation devices	79/956 (8.3%)	Ceftriaxone (SD) 36/990 (3.6%)	0.001

NS = not significant; **SD** = single dose.

Table IV. Prospective trials of antibacterial prophylaxis with active control in bone surgery

Study (year)	Surgical procedure	Rate of infection		p-Value
		short regimen (duration)	long regimen (duration)	
Nelson et al.[52] (1983)	Hip and knee replacement, hip repair	Cefazolin (1 day) 3/186 (1.6%)	Cefazolin (7 days) 4/172 (2.3%)	NS
Gatell et al.[53] (1987)	Type of fixation:	Cefamandole (SD)	Cefamandole (1 day)	
	Moore prosthesis[a]	5/76 (6.6%)	0/74 (0%)	0.03
	other fixation devices	15/306 (5%)	3/261 (1%)	0.006
Wymenga et al.[54] (1992)	Hip replacement	Cefuroxime (SD) 11/1327 (0.83%)	Cefuroxime (1 day) 6/1324 (0.45%)	NS (p = 0.17)
Mauerhan et al.[55] (1994)	Type of arthroplasty:	Cefuroxime (SD)	Cefazolin (3 days)	
	hip replacement	1/187 (0.5%)	2/168 (1.2%)	NS
	knee replacement	1/178 (0.6%)	3/207 (1.4%)	NS
Nungu et al.[56] (1995)	Hip repair fixation devices	Cefuroxime (1 day) 6/210 (3%)	Cefadroxil (1 day PO) 1/242 (0.4%)	NS (p = 0.07)

a Partial hip prosthesis for fractures of the neck of the femur.

NS = not significant; **PO** = oral; **SD** = single dose.

in the cefalotin (cephalothin) arm. The reduction in the cefalotin arm was significant ($p < 0.03$). However, the overall incidence of infection in this study was only 9%, suggesting that only a few grade III open fractures were included. In all three studies a significant reduction of the infection frequency was observed, indicating that in internal fixation of open fractures pre-emptive therapy with an intravenous first- or second-generation cephalosporin over 5–10 days is appropriate.[57-59] There are no studies on the optimal duration of pre-emptive therapy. In addition, it is not clear whether a 1-day prophylaxis would be adequate for open fractures of grade I and II. At our institution, a 5-day pre-emptive therapy course with amoxicillin/clavulanic acid is used only in patients with grade III open fractures, whereas a ≤1-day prophylaxis with cefuroxime is used in all other types of fracture-fixation surgery.

2.2.5 Guidelines for Prophylaxis

From the different controlled studies, the following guidelines can be drawn. For arthroplasty or internal fixation devices of closed fractures in centres with infection rates <5%, a single dose of intravenous cefamandole (2g 60–30 minutes before incision) or cefuroxime (1.5g 60–30 minutes before incision) is a reasonable option. In centres with unknown or high infection rates (>5%) and in open fractures grade I and grade II, a 1-day prophylaxis regimen should be preferred: intravenous cefuroxime (1.5g 30–60 minutes before incision, followed by two doses of 0.75g every 8 hours) or cefamandole (2g 30–60 minutes before incision, followed by three doses of 1g every 6 hours) are good options. In patients with internal fixation of grade III open fractures, pre-emptive therapy with an antistaphylococcal drug such as intravenous amoxicillin/clavulanic acid (2.2g every 8 hours) or cefuroxime (1.5g, followed by 0.75g every 8 hours) over 5–7 days is reasonable, but not evidence based.

2.2.6 Controversial Issues

There is little evidence to suggest that newer agents with a broader *in vitro* antibacterial spectrum have any advantage over narrower-spectrum cephalosporins. It should be the rule to choose a spectrum as narrow as possible. Newer antibacterials should be reserved for treatment. An excellent study by Boxma et al.[50] breaks this rule by using ceftriaxone, a third-generation cephalosporin. Compared with the different regimens with older cephalosporins, this agent has no advantage, except for the fact that it results in efficacious tissue concentrations during 24 hours, thus providing 1-day coverage in a single dose. However, we prefer the use of a second-generation cephalosporin (e.g. cefuroxime or cefamandole) that can be given as a single dose in centres with low infection rates and in three doses in centres with high or unknown rates of infection.

Newer fluoroquinolones have better activity against Gram-positive cocci (e.g. levofloxacin, moxifloxacin, gatifloxacin), but they should not be used in surgical prophylaxis because of the rapid emergence of resistant staphylococci.[60] In addition, fluoroquinolones combined with rifampicin

(rifampin) are important drugs in the treatment of device-associated infection and, therefore, should be strictly reserved for treatment.[2,60]

Glycopeptides in prophylaxis should be reserved for institutions with a high prevalence of MRSA, to prevent emergence of vancomycin-resistant staphylococci and enterococci.[39] The same applies for linezolid and daptomycin, which should be used only for the treatment of patients with methicillin-resistant staphylococci or multiresistant enterococci.[61] Dalbavancin is a novel glycopeptide with a long half-life (9–12 days) and excellent *in vitro* activity against *S. aureus* and coagulase-negative staphylococci.[62,63] Thus, dalbavancin has the potential for prophylaxis of device-associated infections. In a rabbit catheter model, dalbavancin proved its efficacy for prevention of *S. aureus* infection.[64] However, there is no need for an antibacterial agent used in prophylaxis to remain in blood for >1 week; usually a half-life of up to 4 hours is sufficient.

2.3 Prophylaxis of Late Haematogenous Infections

The occurrence of haematogenous prosthetic joint infection is experimentally and clinically well established.[21,65-70] During experimental bacteraemia, selective seeding of *S. aureus* on subcutaneous implants has been shown. After an experimental bacteraemia of 10^2–10^3 cfu *S. aureus*/mL of blood, persistent extravascular implant-associated infection occurred in 42%, whereas no single visceral infection could be detected in the same guinea pigs.[69] In a recent cohort study of 40 consecutive episodes of prosthetic knee-associated infection, the fraction of haematogenous infections has been estimated at 38%.[24] The combined incidence rates of knee and hip arthroplasty-associated infections is considerably higher during the first 2 years than between the third and tenth year after surgery (5.9 vs 2.3 per 1000 joint-years).[71] Thus, haematogenous seeding occurs during the patient's entire life; however, the risk is highest early after implantation. These data do not imply that routine antibacterial prophylaxis is needed during procedures potentially causing bacteraemia. Whereas multiple publications illustrate the occurrence of prosthetic joint infection after clinically documented infection, convincing evidence of haematogenous seeding during dental treatment procedures is still lacking.[21,66,70,72,73] Following dental work, in no case have genetically identical strains of streptococci in the mouth and the joint been documented. The infection rate by oral microorganisms of prosthetic joints has been estimated as 0.05%.[74] Since the risk of a bacteraemia from periodontitis, oral hygiene and mastication is considerably higher than from dental treatment, the routine use of antibacterial prophylaxis during procedures with potential bacteraemia is not recommended.[75] Accordingly, the American Dental Association/Academy of Orthopaedic surgeons (AAOS) has published advisory statements which state that antibacterial prophylaxis is not mandatory during dental procedures, but it should be considered in patients with increased risk of haematogenous prosthetic joint infection, such as early after joint replacement (within 1 year after implantation), in immunocompromised patients and in those with severe co-morbidities (especially in patients with underlying inflammatory arthropathies).[76,77] For these patients, a single-dose prophylaxis with oral amoxicillin (2g 1 hour prior to the dental procedure) or oral clindamycin (600mg 1 hour prior to the dental procedure) has been suggested.

In our view, it is more important to minimise the risk of bacteraemia during dental procedures than to administer prophylaxis before dental treatment. This strategy includes elimination of potential infectious foci prior to arthroplasty (such as dental treatment of parodontitis or root infection), avoidance of clean-contaminated surgery (such as transurethral prostatectomy or tonsillectomy) during the first year after joint replacement, and rapid diagnosis and treatment of any infection in patients with prosthetic joints. The most frequent sources of haematogenous infection are infections of the skin and soft tissues, oral cavity (parodontitis), urinary tract and respiratory tract.[72] In a prospective study of 80 patients with orthopaedic implants and documented *S. aureus* bacteraemia, the risk of haematogenous seeding was 34% in patients with prosthetic joints and 7% in those with internal fixation devices.[21] In 25% of these patients, no primary focus could be found. This suggests that in patients with orthopaedic implants experiencing clinical sepsis, rapid antibacterial treatment is important. This empirical intravenous antibacterial should be active against staphylococci.

We suggest either intravenous (flu-)cloxacillin (2g every 6 hours) or intravenous vancomycin (1g every 12 hours), depending on the prevalence of MRSA. Before initiation of treatment, blood cultures should be drawn and, thereafter, daily examination for signs of possible prosthetic joint infection should be made.

2.4 Active Immunisation against *S. aureus*

An attractive concept for prophylaxis of implant-associated infections is active immunisation against frequently involved microorganisms. A polysaccharide conjugate vaccine against *S. aureus* (StaphVAX®)[1] efficaciously prevented bloodstream infections in patients with end-stage renal disease who were receiving haemodialysis.[78] Furthermore, patients vaccinated prior to an orthopaedic procedure demonstrated protective antibodies against *S. aureus*, preventing postoperative bacteraemia. Whether these antibodies would also protect against colonisation of an implanted device has not been investigated. On 1 November 2005, the manufacturer of StaphVAX® (Nabi Biopharmaceuticals, Boca Raton, CA; www.nabi.com) announced a failure of a confirmatory phase III clinical trial to prevent *S. aureus* bloodstream infection. Thus, a combination vaccine against *S. aureus* and coagulase-negative staphylococci for clinical use will probably not be available in the near future.

Another strategy for prevention would be the elimination of *S. aureus* nasal carriage by vaccination. Such a vaccine has proved to be effective in the cotton rat model.[79]

3. Treatment

3.1 General Principles and Surgical Options

3.1.1 Treatment Goals

In prosthetic joint infections the treatment goal is eradication of infection, leading to a satisfactory pain-free and functional joint.[2] In contrast to prosthetic joint infections, the primary aim in infections associated with fracture fixation devices is consolidation of the fracture and prevention of subsequent chronic osteomyelitis.[80] Thus, complete eradication of microorganisms in fracture fixation device-associated infections is not always necessary, since the device can be removed after the bone is consolidated. An algorithm for treatment of implant-associated infections has recently been published.[2,80,81] These recommendations consider the type and susceptibility of the pathogen, duration of symptoms, stability of the implant and the condition of the surrounding tissue.

3.1.2 Principal Treatment Options

Eradication of infection can be generally accomplished only with a combination of both an appropriate surgical treatment and antimicrobial treatment. Five treatment approaches are available:

1. *Long-term antimicrobial therapy alone* (i.e. without concomitant surgery at the implant site) controls clinical manifestations, but rarely eradicates the infection; in most patients, clinical symptoms recur after antibacterial discontinuation.[71] Therefore, this option may be chosen if surgery is contraindicated, a functional prosthesis is not needed (e.g. a bedridden patient) or the patient refuses surgical intervention.[2]
2. *Debridement with implant retention* is a reasonable option for patients with an early postoperative or acute haematogenous infection, if the duration of clinical signs and symptoms is <3 weeks, the implant is stable, the soft tissue is in good condition and an agent with activity against biofilm microorganisms is available (see antibacterial treatment in section 3.2).[60,82-85] Thus, rapid diagnosis of infection, early debridement, early antimicrobial therapy, the stability of the implant and the type of microorganism are crucial.
3. *One-stage prosthesis exchange* includes removal and implantation of a new device during the same surgical procedure. This approach is recommended if the patient has no severe co-morbidity, the surrounding soft tissue is in good condition and difficult-to-treat microorganisms (such as MRSA or other multiresistant bacteria, small-colony variants of staphylococci, enterococci or fungi) are not involved.[86-89]
4. *Two-stage prosthesis exchange* includes removal of the prosthesis with implantation of a new prosthe-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

sis during a later surgical procedure. This modality is preferred in patients with severely compromised soft tissue.[2,81,90-93] The interval until reimplantation can be short (2–4 weeks) or long (8 weeks). A temporary spacer or an external fixation device can be placed to secure the length of the limb. If difficult-to-treat microorganisms are causing the infection, a long interval before reimplantation and no placement of a spacer are suggested to optimise the treatment success.

5. *Permanent removal of the implant* or *arthrodesis* is usually performed in severely immunocompromised patients, those with active intravenous drug use and when arthroplasty does not provide any functional benefit.

3.2 Established Antibacterial Agents

3.2.1 Selection of Antibacterial Regimen

Table V summarises suggested antibacterial regimens according to the pathogen and its antibacterial susceptibility. The optimal antibacterial therapy is well established in staphylococcal implant-associated infections. Rifampicin has demonstrated good activity on slow-growing and adherent staphylococci *in vitro*, in experimental animal models,[83-85] and in clinical studies.[24,25,60,82,94,95] It must always be combined with another drug to prevent emergence of resistance. For the initial intravenous treatment, a β-lactam (e.g. cloxacillin, flucloxacillin, nafcillin, cefazolin) or a glycopeptide (e.g. vancomycin or teicoplanin) is typically used for 2 weeks, depending on the susceptibility of the infecting organism. In a randomised placebo-controlled study, patients were treated with debridement and retention combined with either oral ciprofloxacin plus placebo or ciprofloxacin plus rifampicin (following the initial intravenous treatment).[60] The cure rate was 100% in those patients who tolerated long-term therapy with ciprofloxacin plus rifampicin compared with 58% in those treated with ciprofloxacin alone.

Vancomycin has lower antibacterial activity against Gram-positive microorganisms than β-lactams, and should only be used when β-lactams are contraindicated because of resistance or hypersensitivity. Nephrotoxicity, ototoxicity, thrombophlebitis and neutropenia are the major adverse effects limiting its use. However, in a meta-analysis of randomised controlled trials, clinical failure was lower in patients receiving continuous infusion (30 mg/kg/day) than conventional intermittent infusion (15 mg/kg every 12 hours), whereas no differences were found regarding mortality and nephrotoxicity.[96] The data suggest that the administration of the same total antibacterial dose by continuous intravenous infusion may be more efficient than the intermittent mode; however, the stability of the drug exposed to environmental conditions for up to 24 hours, a higher risk of catheter-associated infections and the potential incompatibility with other coadministered drugs may be limitations of continuous infusions.

Fluoroquinolones are excellent drugs to combine with rifampicin against staphylococci, because of their good bioavailability, activity and safety; however, they can rarely eliminate adherent staphylococci when given alone.[85] Newer fluoroquinolones (such as moxifloxacin, levofloxacin and gatifloxacin) have an improved activity against staphylococci and were studied in experimental bone or implant-associated infections;[97,98] however, only anecdotal clinical data exist with these new drugs.[24,99,100] In addition, safety data for long-term therapy with moxifloxacin and gatifloxacin are not available. For levofloxacin, long-term experience is only available by extrapolating from the ofloxacin-experience and from studies in patients with mycobacterial infections.[94,101,102] Moreover, possible interactions of newer fluoroquinolones with rifampicin have not yet been systematically assessed. MRSA should not be treated with fluoroquinolones, since antibacterial resistance may emerge during treatment. Other anti-staphylococcal drugs, such as cotrimoxazole, minocycline or fusidic acid, have been combined with rifampicin and may have similar success rates to fluoroquinolones combined with rifampicin.[94] High-dose oral cotrimoxazole was used in one study as monotherapy for treatment of 39 infected orthopaedic implants, with an overall clinical success rate of 67%; however, unstable components were removed several months after initiation of treatment.[103] Only few data are available for the treatment of Gram-negative bacilli. *In vitro* and animal studies demonstrated better efficacy of ciprofloxacin against Gram-negative bacilli than β-lactams.[104]

Table V. Treatment of implant-associated infections (adapted from Zimmerli et al.,[2] with permission)

Microorganism	Antibacterial agent[a]	Dosage	Route
Staphylococcus spp.			
methicillin-susceptible	Rifampicin plus	450mg q12h	PO/IV
	nafcillin or (flu)cloxacillin[b]	2g q6h	IV
	for 2 weeks, followed by		
	rifampicin plus	450mg q12h	PO
	ciprofloxacin or	750mg q12h	PO
	levofloxacin	750mg q24h to 500mg q12h	PO
methicillin-resistant	Rifampicin plus	450mg q12h	PO/IV
	vancomycin	1g q12h[c]	IV
	for 2 weeks, followed by		
	rifampicin plus	450mg q12h	PO
	ciprofloxacin[d] or	750mg q12h	PO
	levofloxacin[d] or	750mg q24h to 500mg q12h	PO
	teicoplanin[e] or	400mg q24h	IV/IM
	fusidic acid or	500mg q8h	PO
	cotrimoxazole or	1 DS tablet q8h[f]	PO
	minocycline	100mg q12h	PO
Streptococcus spp.	Benzylpenicillin[b] or	5MU q6h	IV
	ceftriaxone	2g q24h	IV
	for 4 weeks, followed by		
	amoxicillin	750–1000mg q8h	PO
Enterococcus spp. (penicillin-susceptible)	Benzylpenicillin or	5MU q6h	IV
	ampicillin or amoxicillin	2g q4–6h	IV
	plus aminoglycoside		IV
	for 2–4 weeks, followed by		
	amoxicillin	750–1000mg q8h	PO
Enterobacteriaceae (fluoroquinolone-susceptible)	Ciprofloxacin	750mg q12h	PO
Nonfermenters (e.g. *Pseudomonas aeruginosa*)	Cefepime or ceftazidime plus aminoglycoside[g]	2g q8h	IV
	for 2–4 weeks, followed by		
	ciprofloxacin	750mg q12h	PO
Anaerobes[h]	Clindamycin	600mg q6–8h	IV
	for 2–4 weeks, followed by		
	clindamycin	300mg q6h	PO
Mixed infections (without methicillin-resistant staphylococci)	Amoxicillin/clavulanic acid	2.2g q8h	IV
	or piperacillin/tazobactam	4.5g q8h	IV
	or imipenem	500mg q6h	IV
	or meropenem	1g q8h	IV
	for 2–4 weeks, followed by individual regimens according to antibacterial susceptibility		

a For total duration of antibacterial treatment see section 3.2.2.

b In patients with delayed hypersensitivity, cefazolin (2g q8h IV) can be administered. In patients with immediate hypersensitivity, penicillin should be replaced by vancomycin (1g q12h IV).

c Alternatively, vancomycin may be administered as continuous infusion (30 mg/kg/day).

d Methicillin-resistant *S. aureus* should *not* be treated with fluoroquinolones, since antibacterial resistance may emerge during treatment.

e First 1–3 days of treatment, teicoplanin dose should be increased to 800mg IV.

f DS tablet = trimethoprim 160mg plus sulfamethoxazole 800mg.

g Aminoglycosides can be administered in a single daily dose.

h Alternatively, benzylpenicillin (5MU q6h IV) or ceftriaxone (2g q24h IV) can be used for Gram-positive anaerobes (e.g. *Propionibacterium acnes*), and metronidazole (500mg q8h IV or PO) for Gram-negative anaerobes (e.g. *Bacteroides* spp.).

DS = double strength or forte; **IM** = intramuscular; **IV** = intravenous; **PO** = oral; **qXh** = every X hours.

3.2.2 Duration of Antibacterial Treatment

In patients with prosthesis retention, one-stage exchange or two-stage exchange with a short interval (2–4 weeks), the suggested antibacterial treatment duration is 3 months. Infections associated with prosthetic knees have longer suggested treatment duration (6 months) because of the often unfavourable condition of the surrounding soft tissue. Intravenous treatment should typically be administered for the initial 2–4 weeks, followed by oral therapy to complete the treatment course.

In patients with two-stage exchange with a long interval (8 weeks) and without a spacer, the aim of antibacterial therapy is complete elimination of infection in the absence of any foreign material. Intravenous treatment is given for 6 weeks after removal of the prosthesis. Two weeks before reimplantation of the prosthesis, antibacterial treatment is discontinued in order to obtain reliable tissue specimens for culture and histopathology at the time of reimplantation. If these specimens show no growth and no acute inflammation, antibacterial treatment can be discontinued; otherwise it is continued for a total of 3 months (or 6 months in knee prostheses).

In fracture-fixation devices, the treatment duration is 3 months when the device is retained and 6 weeks when there is complete removal of all hardware.[60,80] If no antibacterial with efficacy on adherent bacteria is available (see section 3.2.1), treatment with implant retention is generally only suppressive, until the implants can definitively be removed. In such situations, antibacterials should be continued for at least 2 weeks after removal of all implants, in order to avoid development of chronic osteomyelitis.

3.3 Newer and Investigational Antimicrobial Agents

Quinupristin/dalfopristin is a streptogramin antibacterial active against *S. aureus* (including MRSA) and *Enterococcus faecium* (including vancomycin-resistant strains), but not against *E. faecalis*. In a rabbit model of knee prosthesis infection with MRSA, quinupristin/dalfopristin (30 mg/kg every 8 hours), but not vancomycin (60 mg/kg every 12 hours), significantly reduced the mean log cfu of *S. aureus* per gram of bone compared with controls.[105] Furthermore, the combination of quinupristin/dalfopristin with rifampicin (10 mg/kg every 12 hours) was significantly more effective than quinupristin/dalfopristin or vancomycin alone. In a study of 40 patients with orthopaedic infections with MRSA (6 of whom had an orthopaedic prosthesis), clinical success was reported in 78% and microbial eradication in 69%.[106]

Linezolid is the first member of the oxazolidinones, active against virtually all Gram-positive cocci, including methicillin-resistant staphylococci and vancomycin-resistant enterococci (VRE). It can be administered intravenously or orally with 100% bioavailability. In a retrospective study, 20 consecutive patients receiving linezolid for orthopaedic infections (15 of whom had an orthopaedic device) were evaluated.[61] At a mean follow-up of 276 days, 55% achieved clinical cure and 35% had clinical improvement but received long-term suppressive antibacterial therapy with linezolid. Importantly, reversible myelosuppression occurred in 40% of patients during treatment and irreversible peripheral neuropathy in 5%. Only limited data on linezolid in combination with rifampicin are available. In time-kill experiments, linezolid showed an additive effect on MRSA when combined with rifampicin.[107]

RWJ-416457 is a novel pyrrolopyrazolyl-substituted oxazolidinone with at least 2- to 4-fold higher *in vitro* activity than linezolid against *S. aureus* (including MRSA and vancomycin-intermediate strains [VISA]), enterococci (including VRE) and streptococci.[108] In a mouse systemic infection model, RWJ-416457 was more potent than linezolid against methicillin-susceptible *S. aureus* (MSSA) and at least equipotent against MRSA.[109]

Daptomycin (formerly LY146032) is a cyclic lipopeptide with activity against Gram-positive bacteria, including MRSA, vancomycin-resistant *S. aureus* and VRE.[110,111] In a retrospective study of Gram-positive bone and joint infections without implants (including eight patients with MRSA) and treated with daptomycin for 8–44 days, resolution of signs and symptoms was achieved at the time of hospital discharge in 8 of 9 patients.[112] However, no post-discharge follow-up was performed. In an animal model of implant-associated infections, daptomycin showed no advantage compared with vancomycin or teicoplanin.[83] The low cure rate in tissue-cage infections may be correlated with a 6-

fold increase of the stationary-phase minimum bactericidal concentration (MBC) of *S. epidermidis* (from 2 μg/mL to 12.5 μg/mL). In addition, daptomycin had a low activity on adherent staphylococci *in vitro* and in the tissue-cage infection model.[113] Synergy between daptomycin and both rifampicin and β-lactams was found against VRE and MRSA *in vitro*, but further studies are needed to elucidate the mechanisms and to determine the *in vivo* efficacy of the combination.[114,115] As an intravenous agent that is administered once per day, daptomycin offers a possibility for outpatient therapy. Development of daptomycin resistance and treatment failure was recently reported in two patients with osteomyelitis due to MRSA. In both patients, disk diffusion susceptibility testing failed to detect resistance.[116]

Dalbavancin (formerly BI 397) is a novel semisynthetic derivative of teicoplanin-like glycopeptide A40926, which is more active *in vitro* against methicillin-susceptible and -resistant staphylococci than vancomycin or teicoplanin. Against streptococci, dalbavancin had activity comparable to that of teicoplanin, but better than that of vancomycin.[117] In one study, minimum concentration to inhibit growth of 90% of isolates (MIC_{90}) values of *S. aureus* and coagulase-negative staphylococci (0.06 μg/mL) were considerably lower than those of vancomycin (1–2 μg/mL), teicoplanin (1–16 μg/mL), daptomycin (0.5 μg/mL) and linezolid (2–4 μg/mL).[63] Dalbavancin was bactericidal against all six tested staphylococcal strains at four times the MIC. Dalbavancin has a long half-life (9–12 days) that may allow a once-weekly dose administration.[62]

Tigecycline (formerly GAR-936) is the first member of the glycylcyclines, a novel class of antimicrobials structurally related to tetracyclines (a 9-glycylamido derivative of minocycline).[118,119] It has broad-spectrum activity against aerobic Gram-positive and Gram-negative, anaerobic and atypical pathogens, including MRSA and coagulase-negative staphylococci, penicillin- and quinolone-resistant *Streptococcus pneumoniae*, VRE and extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.[120] Tigecycline is only available as an intravenous agent and distributes extensively in tissues. It has demonstrated good therapeutic response in animal infection models of pneumonia, endocarditis and peritonitis, and in phase III clinical trials involving intra-abdominal and skin and soft tissue infections. The activity of tigecycline was evaluated against *S. epidermidis* growing in an *in vitro* biofilm model.[121] The killing activity of tigecycline against the adherent *S. epidermidis* was at least 4-fold better than that of vancomycin or daptomycin, demonstrating MBC values of 1–8 μg/mL. Furthermore, efficacy of tigecycline (14 mg/kg twice daily subcutaneously) and vancomycin (30 mg/kg twice daily subcutaneously) was evaluated with and without rifampicin (40 mg/kg twice daily orally) in a rabbit model of MRSA osteomyelitis.[122] Tigecycline and rifampicin cleared the infection in bone in 100%, tigecycline alone in 90%, vancomycin alone in 82% and untreated controls in 26%. Tigecycline is a promising agent for treatment of infections with multiresistant pathogens. However, tigecycline (and possible combination regimens with rifampicin or its derivatives) has not yet been evaluated in implant-associated infections.

BP-102 is a new carbacephem antibacterial with potent bactericidal activity against Gram-positive cocci. The MIC_{90} values were 0.25 μg/mL, 2 μg/mL and 4 μg/mL for MSSA, MRSA and methicillin-resistant coagulase-negative staphylococci, respectively.[123] BP-102 also exhibited a potent bactericidal activity against both MSSA and MRSA in the neutropenic murine thigh-infection model.[124]

Novel rifamycin derivatives (such as ABI-0043, ABI-0369 and ABI-0699) have potent *in vitro* activity against Gram-positive cocci, including MRSA and streptococci. These agents have potential advantages over rifampicin, including lower MIC values against staphylococci and streptococci, longer elimination half-lives and no significant interactions with liver microsomal enzymes (cytochrome P450 system). Other attractive characteristics are high intracellular concentrations and large volume of distributions. In a guinea-pig foreign-body infection model, intraperitoneal ABI-0043 (12.5 mg/kg every 12 hours) and rifampicin (12.5 mg/kg every 12 hours) in combination with levofloxacin (5 mg/kg every 12 hours) had similar treatment efficacy against *S. aureus* (100% and 75%, respectively).[125] Thus, ABI-0043 in combination with a fluoroquinolone has the potential to treat staphylococcal implant-associated infections. Importantly, the risk of

emergence of resistance during treatment is considerable, particularly among staphylococci. Thus, similarly to rifampicin, these drugs should not be used as single-agent therapy for treatment of staphylococcal infections. However, there is not complete cross-resistance. Recently developed novel rifamycin derivatives retained some activity against rifampicin-resistant *S. aureus* mutants in a mouse septicaemia model.[126-128]

4. Conclusions

Prophylaxis and treatment of infections associated with orthopaedic devices have improved during the last decade. For perioperative prophylaxis, a first- or second-generation cephalosporin (such as cefazolin, cefamandole or cefuroxime) is recommended. The prophylactic agent should be administered between 60 and 30 minutes before incision either as a single dose or continued for 24 hours. If the patient is allergic to cephalosporins, or in settings with high prevalence of MRSA, vancomycin or teicoplanin are alternative options. If a tourniquet is used, antibacterial prophylaxis should be administered at least 10 minutes before inflation of the tourniquet. In open fractures, pre-emptive therapy with a first- or second-generation cephalosporin or amoxicillin/clavulanic acid over 5–10 days is recommended.

Treatment of infections associated with orthopaedic devices usually requires appropriate surgical intervention combined with a prolonged antimicrobial therapy. The choice of the antimicrobial regimen depends on duration and pathogenesis of infection, stability of the implant, antimicrobial susceptibility of the pathogen and the condition of the surrounding soft tissue. The optimal antibacterial therapy is well established in staphylococcal implant-associated infections, and includes rifampicin in combination with β-lactams, glycopeptides, fluoroquinolones, minocycline, cotrimoxazole or fusidic acid. Increasing antibacterial resistance requires the use of alternative agents, such as quinupristin/dalfopristin, linezolid and daptomycin, but there are limited results from clinical trials with these agents. Potential new antibacterial agents, which are currently still investigational, include a novel oxazolidinone (RWJ-416457), a glycopeptide (dalbavancin), a glycylcycline compound (tigecycline), a new carbacephem (BP-102), and rifamycin derivatives such as ABI-0043.

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References

1. Darouiche RO. Treatment of infections associated with surgical implants. N Engl J Med 2004; 350: 1422-9
2. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med 2004; 351: 1645-54
3. McGraw JM, Lim EV. Treatment of open tibial-shaft fractures: external fixation and secondary intramedullary nailing. J Bone Joint Surg Am 1988; 70: 900-11
4. Obremskey WT, Bhandari M, Dirschl DR, et al. Internal fixation versus arthroplasty of comminuted fractures of the distal humerus. J Orthop Trauma 2003; 17: 463-5
5. Perren SM. Evolution of the internal fixation of long bone fractures: the scientific basis of biological internal fixation: choosing a new balance between stability and biology. J Bone Joint Surg Br 2002; 84: 1093-110
6. Raahave D. Postoperative wound infection after implant and removal of osteosynthetic material. Acta Orthop Scand 1976; 47: 28-35
7. Zimmerli W. Antibiotic prophylaxis. In: Ruedi RP, Murphy WM, editors. AO Principles of fracture management. Stuttgart, Germany: Thieme, 2006. In press
8. Brause BD. Infections with prostheses in bones and joints. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th ed. Washington, DC: WB Saunders, 2005: 1332-7
9. Darouiche RO. Device-associated infections: a macroproblem that starts with microadherence. Clin Infect Dis 2001; 33: 1567-72
10. Trampuz A, Osmon DR, Hanssen AD, et al. Molecular and antibiofilm approaches to prosthetic joint infection. Clin Orthop 2003; 414: 69-88
11. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science 1999; 284: 1318-22
12. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet 2001; 358: 135-8
13. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis 2002; 8: 881-90
14. Zimmerli W, Waldvogel FA, Vaudaux P, et al. Pathogenesis of foreign body infection: description and characteristics of an animal model. J Infect Dis 1982; 146: 487-97
15. Willenegger H, Roth B. Treatment tactics and late results in early infection following osteosynthesis [in German]. Unfallchirurgie 1986; 12: 241-6
16. Ochsner PE, Sirkin MS, Trampuz A. Acute infection. In: Ruedi RP, Murphy WM, editors. AO principles of fracture management [in press]. Stuttgart, Germany: Thieme, 2006
17. Arens S, Hansis M, Schlegel U, et al. Infection after open reduction and internal fixation with dynamic compression plates: clinical and experimental data. Injury 1996; 27 Suppl. 3: SC27-33
18. Arens S, Kraft C, Schlegel U, et al. Susceptibility to local infection in biological internal fixation: experimental study of open vs minimally invasive plate osteosynthesis in rabbits. Arch Orthop Trauma Surg 1999; 119: 82-5

19. Benson DR, Riggins RS, Lawrence RM, et al. Treatment of open fractures: a prospective study. J Trauma 1983; 23: 25-30
20. Law MD, Stein RE. Late infection in healed fractures after open reduction and internal fixation. Orthop Rev 1993; 22: 545-52
21. Murdoch DR, Roberts SA, Fowler JV, et al. Infection of orthopedic prostheses after *Staphylococcus aureus* bacteremia. Clin Infect Dis 2001; 32: 647-9
22. Spangehl MJ, Masri BA, O'Connell JX, et al. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. J Bone Joint Surg Am 1999; 81: 672-83
23. Widmer AF. New developments in diagnosis and treatment of infection in orthopedic implants. Clin Infect Dis 2001; 33 Suppl. 2: 94-106
24. Laffer RR, Graber P, Ochsner PE, et al. Outcome of prosthetic knee-associated infection: evaluation of 40 consecutive episodes of a single center. Clin Microbiol Infect 2006; 12: 433-9
25. Giulieri SG, Graber P, Ochsner PE, et al. Management of infection associated with total hip arthroplasty according to a treatment algorithm. Infection 2004; 32: 222-8
26. Trampuz A, Hanssen AD, Osmon DR, et al. Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infection. Am J Med 2004; 117: 556-62
27. von Eiff C, Becker K, Machka K, et al. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. N Engl J Med 2001; 344: 11-6
28. Kalmeijer MD, Coertjens H, Nieuwland-Bollen PM, et al. Surgical site infections in orthopedic surgery: the effect of mupirocin nasal ointment in a double-blind, randomized, placebo-controlled study. Clin Infect Dis 2002; 35: 353-8
29. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. N Engl J Med 2002; 346: 1871-7
30. Elek SD, Conen PE. The virulence of Staphylococcus pyrogenes for man: a study of the problem of wound infection. Br J Exp Pathol 1957; 38: 573-86
31. Zimmerli W, Lew PD, Waldvogel FA. Pathogenesis of foreign body infection: Evidence for a local granulocyte defect. J Clin Invest 1984; 73: 1191-200
32. Kaiser AB. Antimicrobial prophylaxis in surgery. N Engl J Med 1986; 315: 1129-38
33. Cruse PJ, Foord R. The epidemiology of wound infection: a 10-year prospective study of 62,939 wounds. Surg Clin North Am 1980; 60: 27-40
34. Haas DW, Kaiser AB. Antimicrobial prophylaxis of infections associated with foreign bodies. In: Bisno AL, Waldvogel FA, editors. Infections associated with indwelling medical devices. 3rd ed. Washington, DC: American Society for Microbiology, 2000: 395-406
35. Dellinger EP, Gross PA, Barrett TL, et al. Quality standard for antimicrobial prophylaxis in surgical procedures. The Infectious Diseases Society of America. Infect Control Hosp Epidemiol 1994; 15: 182-8
36. Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma 1984; 24: 742-6
37. 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: 471-8
38. Chin NX, Neu NM, Neu HC. Activity of cephalosporins against coagulase-negative staphylococci. Diagn Microbiol Infect Dis 1990; 13: 67-9
39. Anon. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 1995; 44: 1-13
40. Suter F, Avai A, Fusco U, et al. Teicoplanin versus cefamandole in the prevention of infection in total hip replacement. Eur J Clin Microbiol Infect Dis 1994; 13: 793-6
41. Burke JP. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery 1961; 50: 161-8
42. Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992; 326: 281-6
43. Widmer AF, Weber W, Reck N, et al. <30 Minutes before incision is too late: new insights for timing of antimicrobial prophylaxis from 4557 patients [abstract]. 45th ICAAC, American Society for Microbiology; 2005 Dec 16-19; Washington, DC. 2005; K-1370
44. Friedman RJ, Friedrich LV, White RL, et al. Antibiotic prophylaxis and tourniquet inflation in total knee arthroplasty. Clin Orthop Relat Res 1990; (260): 17-23
45. Oishi CS, Carrion WV, Hoaglund FT. Use of parenteral prophylactic antibiotics in clean orthopaedic surgery: a review of the literature. Clin Orthop Relat Res 1993; (296): 249-55
46. Hill C, Flamant R, Mazas F, et al. Prophylactic cefazolin versus placebo in total hip replacement: report of a multicentre double-blind randomised trial. Lancet 1981; I: 795-6
47. Gatell JM, Riba J, Lozano ML, et al. Prophylactic cefamandole in orthopaedic surgery. J Bone Joint Surg Am 1984; 66: 1219-22
48. Bodoky A, Neff U, Heberer M, et al. Antibiotic prophylaxis with two doses of cephalosporin in patients managed with internal fixation for a fracture of the hip. J Bone Joint Surg Am 1993; 75: 61-5
49. Paiement GD, Renaud E, Dagenais G, et al. Double-blind randomized prospective study of the efficacy of antibiotic prophylaxis for open reduction and internal fixation of closed ankle fractures. J Orthop Trauma 1994; 8: 64-6
50. Boxma H, Broekhuizen T, Patka P, et al. Randomised controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: the Dutch Trauma Trial. Lancet 1996; 347: 1133-7
51. Gillespie WJ, Walenkamp G. Antibiotic prophylaxis for surgery for proximal femoral and other closed long bone fractures. Cochrane Database Syst Rev 2001; (1): CD000244
52. Nelson CL, Green TG, Porter RA, et al. One day versus seven days of preventive antibiotic therapy in orthopedic surgery. Clin Orthop Relat Res 1983; (176): 258-63
53. Gatell JM, Garcia S, Lozano L, et al. Perioperative cefamandole prophylaxis against infections. J Bone Joint Surg Am 1987; 69: 1189-93
54. Wymenga A, van Horn J, Theeuwes A, et al. Cefuroxime for prevention of postoperative coxitis: one versus three doses tested in a randomized multicenter study of 2,651 arthroplasties. Acta Orthop Scand 1992; 63: 19-24
55. Mauerhan DR, Nelson CL, Smith DL, et al. Prophylaxis against infection in total joint arthroplasty: one day of cefuroxime compared with three days of cefazolin. J Bone Joint Surg Am 1994; 76: 39-45
56. Nungu KS, Olerud C, Rehnberg L, et al. Prophylaxis with oral cefadroxil versus intravenous cefuroxime in trochanteric fracture surgery: a clinical multicentre study. Arch Orthop Trauma Surg 1995; 114: 303-7
57. Patzakis MJ, Harvey JP, Ivler D. The role of antibiotics in the management of open fractures. J Bone Joint Surg Am 1974; 56: 532-41
58. Braun R, Enzler MA, Rittmann WW. A double-blind clinical trial of prophylactic cloxacillin in open fractures. J Orthop Trauma 1987; 1: 12-7
59. Tscherne H, Oestern HJ, Sturm J. Osteosynthesis of major fractures in polytrauma. World J Surg 1983; 7: 80-7

60. Zimmerli W, Widmer AF, Blatter M, et al. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA 1998; 279: 1537-41
61. Razonable RR, Osmon DR, Steckelberg JM. Linezolid therapy for orthopedic infections. Mayo Clin Proc 2004; 79: 1137-44
62. Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. Clin Infect Dis 2005; 40: 374-80
63. Lin G, Credito K, Ednie LM, et al. Antistaphylococcal activity of dalbavancin, an experimental glycopeptide. Antimicrob Agents Chemother 2005; 49: 770-2
64. Darouiche RO, Mansouri MD. Dalbavancin compared with vancomycin for prevention of *Staphylococcus aureus* colonization of devices in vivo. J Infect 2005; 50: 206-9
65. Southwood RT, Rice JL, McDonald PJ, et al. Infection in experimental hip arthroplasties. J Bone Joint Surg Br 1985; 67: 229-31
66. Ahlberg A, Carlsson AS, Lindberg L. Hematogenous infection in total joint replacement. Clin Orthop Relat Res 1978; (137): 69-75
67. Blomgren G, Lindgren U. Late hematogenous infection in total joint replacement: studies of gentamicin and bone cement in the rabbit. Clin Orthop Relat Res 1981; (155): 244-8
68. Blomgren G. Hematogenous infection of total joint replacement: an experimental study in the rabbit. Acta Orthop Scand Suppl 1981; 187: 1-64
69. Zimmerli W, Zak O, Vosbeck K. Experimental hematogenous infection of subcutaneously implanted foreign bodies. Scand J Infect Dis 1985; 17: 303-10
70. Kaandorp CJ, Dinant HJ, van de Laar MA, et al. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. Ann Rheum Dis 1997; 56: 470-5
71. Steckelberg JM, Osmon DR. Prosthetic joint infection. In: Bisno AL, Waldvogel FA, editors. Infections associated with indwelling medical devices. 3rd ed. Washington, DC: American Society for Microbiology, 2000: 173-209
72. Maderazo EG, Judson S, Pasternak H. Late infections of total joint prostheses: a review and recommendations for prevention. Clin Orthop 1988; (229): 131-42
73. Bartzokas CA, Johnson R, Jane M, et al. Relation between mouth and haematogenous infection in total joint replacements. BMJ 1994; 309: 506-8
74. Jacobsen PL, Murray W. Prophylactic coverage of dental patients with artificial joints: a retrospective analysis of thirty-three infections in hip prostheses. Oral Surg Oral Med Oral Pathol 1980; 50: 130-3
75. Pallasch TJ, Wahl MJ. Focal infection: new age or ancient history. Endodontic Topics 2003; 4: 32-45
76. American Academy of Orthopaedic Surgeons. Antibiotic prophylaxis for dental patients with total joint replacements (Doc. No. - 1014) [online]. Available from URL: http://www.aaos.org/wordhtml/papers/advistmt/1014.htm [Accessed 2006 Mar 30]
77. American Academy of Orthopaedic Surgeons. Antibiotic prophylaxis for urological patients with total joint replacements (Doc. No. - 1023) [online]. Available from URL: http:// www.aaos.org/wordhtml/papers/advistmt/1023.htm [Accessed 2006 Mar 30]
78. Shinefield H, Black S, Fattom A, et al. Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. N Engl J Med 2002; 346: 491-6
79. Clarke SR, Brummell KJ, Horsburgh MJ, et al. Identification of in vivo-expressed antigens of *Staphylococcus aureus* and their use in vaccinations for protection against nasal carriage. J Infect Dis 2006; 193: 1098-108
80. Trampuz A, Zimmerli W. Diagnosis and treatment of infections associated with fracture fixation devices. Injury 2006; 37 Suppl. 2: S55-66
81. Zimmerli W, Ochsner PE. Management of infection associated with prosthetic joints. Infection 2003; 31: 99-108
82. Widmer AF, Gaechter A, Ochsner PE, et al. Antimicrobial treatment of orthopedic implant-related infections with rifampin combinations. Clin Infect Dis 1992; 14: 1251-3
83. Widmer AF, Frei R, Rajacic Z, et al. Correlation between in vivo and in vitro efficacy of antimicrobial agents against foreign body infections. J Infect Dis 1990; 162: 96-102
84. Zimmerli W, Frei R, Widmer AF, et al. Microbiological tests to predict treatment outcome in experimental device-related infections due to *Staphylococcus aureus*. J Antimicrob Chemother 1994; 33: 959-67
85. Schwank S, Rajacic Z, Zimmerli W, et al. Impact of bacterial biofilm formation on in vitro and in vivo activities of antibiotics. Antimicrob Agents Chemother 1998; 42: 895-8
86. Ure KJ, Amstutz HC, Nasser S, et al. Direct-exchange arthroplasty for the treatment of infection after total hip replacement: an average ten-year follow-up. J Bone Joint Surg Am 1998; 80: 961-8
87. Hope PG, Kristinsson KG, Norman P, et al. Deep infection of cemented total hip arthroplasties caused by coagulase-negative staphylococci. J Bone Joint Surg Br 1989; 71: 851-5
88. Raut VV, Siney PD, Wroblewski BM. One-stage revision of infected total hip replacements with discharging sinuses. J Bone Joint Surg Br 1994; 76: 721-4
89. Callaghan JJ, Katz RP, Johnston RC. One-stage revision surgery of the infected hip: a minimum 10-year followup study. Clin Orthop 1999; (369): 139-43
90. Langlais F. Can we improve the results of revision arthroplasty for infected total hip replacement? J Bone Joint Surg Br 2003; 85: 637-40
91. Westrich GH, Salvati EA, Brause B. Postoperative infection. In: Bono JV, McCarty JC, Thornhill TS, et al., editors. Revision total hip arthroplasty. 1st ed. New York (NY): Springer, 1999: 371-90
92. Windsor RE, Insall JN, Urs WK, et al. Two-stage reimplantation for the salvage of total knee arthroplasty complicated by infection: further follow-up and refinement of indications. J Bone Joint Surg Am 1990; 72: 272-8
93. Colyer RA, Capello WN. Surgical treatment of the infected hip implant: two-stage reimplantation with a one-month interval. Clin Orthop 1994; (298): 75-9
94. Drancourt M, Stein A, Argenson JN, et al. Oral treatment of *Staphylococcus* spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. J Antimicrob Chemother 1997; 39: 235-40
95. Trebse R, Pisot V, Trampuz A. Treatment of infected retained implants. J Bone Joint Surg Br 2005; 87B: 249-56
96. Kasiakou SK, Sermaides GJ, Michalopoulos A, et al. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis 2005; 5: 581-9
97. Shirtliff ME, Calhoun JH, Mader JT. Comparative evaluation of oral levofloxacin and parenteral nafcillin in the treatment of experimental methicillin-susceptible *Staphylococcus aureus* osteomyelitis in rabbits. J Antimicrob Chemother 2001; 48: 253-8
98. Vaudaux P, Francois P, Bisognano C, et al. Comparison of levofloxacin, alatrofloxacin, and vancomycin for prophylaxis and treatment of experimental foreign-body-associated infection by methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2002; 46: 1503-9
99. Greenberg RN, Newman MT, Shariaty S, et al. Ciprofloxacin, lomefloxacin, or levofloxacin as treatment for chronic osteomyelitis. Antimicrob Agents Chemother 2000; 44: 164-6

100. Frippiat F, Meunier F, Derue G. Place of newer quinolones and rifampicin in the treatment of Gram-positive bone and joint infections. J Antimicrob Chemother 2004; J Antimicrob Chemother 2004 Dec; 54 (6): 1158

101. Yew WW, Chan CK, Leung CC, et al. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. Chest 2003; 124: 1476-81

102. Drancourt M, Stein A, Argenson JN, et al. Oral rifampin plus ofloxacin for treatment of Staphylococcus-infected orthopedic implants. Antimicrob Agents Chemother 1993; 37: 1214-8

103. Stein A, Bataille JF, Drancourt M, et al. Ambulatory treatment of multidrug-resistant Staphylococcus-infected orthopedic implants with high-dose oral co-trimoxazole (trimethoprim-sulfamethoxazole). Antimicrob Agents Chemother 1998; 42: 3086-91

104. Widmer AF, Wiestner A, Frei R, et al. Killing of nongrowing and adherent *Escherichia coli* determines drug efficacy in device-related infections. Antimicrob Agents Chemother 1991; 35: 741-6

105. Saleh-Mghir A, Ameur N, Muller-Serieys C, et al. Combination of quinupristin-dalfopristin (Synercid) and rifampin is highly synergistic in experimental *Staphylococcus aureus* joint prosthesis infection. Antimicrob Agents Chemother 2002; 46: 1122-4

106. Drew RH, Perfect JR, Srinath L, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy: for the Synercid Emergency-Use Study Group. J Antimicrob Chemother 2000; 46: 775-84

107. Jacqueline C, Caillon J, Le M, et al. In vitro activity of linezolid alone and in combination with gentamicin, vancomycin or rifampicin against methicillin-resistant *Staphylococcus aureus* by time-kill curve methods. J Antimicrob Chemother 2003; 51: 857-64

108. Foleno BD, Goldschmidt RM, Flamm R, et al. In vitro antibacterial activity of the pyrrolopyrazolyl-substituted oxazolidinone RWJ-416457 [abstract]. 45th ICAAC, American Society for Microbiology; 2005 Dec 16-19; Washington, DC. 2005: F-1244

109. Hilliard JJ, Melton J, Fernandez J, et al. In vivo activity of the novel oxazolidinone RWJ-416457 [abstract]. 45th ICAAC, American Society for Microbiology; 2005 Dec 16-19; Washington, DC. 2005; F-1247

110. Tedesco KL, Rybak MJ. Daptomycin. Pharmacotherapy 2004; 24: 41-57

111. Carpenter CF, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. Clin Infect Dis 2004; 38: 994-1000

112. Finney MS, Crank CW, Segreti J. Use of daptomycin to treat drug-resistant Gram-positive bone and joint infections. Curr Med Res Opin 2005; 21: 1923-6

113. Blaser J, Vergeres P, Widmer AF, et al. In vivo verification of in vitro model of antibiotic treatment of device-related infection. Antimicrob Agents Chemother 1995; 39: 1134-9

114. Rand KH, Houck H. Daptomycin synergy with rifampicin and ampicillin against vancomycin-resistant enterococci. J Antimicrob Chemother 2004; 53: 530-2

115. Rand KH, Houck HJ. Synergy of daptomycin with oxacillin and other beta-lactams against methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2004; 48: 2871-5

116. Hayden MK, Rezai K, Hayes RA, et al. Development of daptomycin resistance in vivo in methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol 2005; 43: 5285-7

117. Jones RN, Biedenbach DJ, Johnson DM, et al. In vitro evaluation of BI 397, a novel glycopeptide antimicrobial agent. J Chemother 2001; 13: 244-54

118. Pankey GA. Tigecycline. J Antimicrob Chemother 2005; 56: 470-80

119. Rubinstein E, Vaughan D. Tigecycline: a novel glycylcycline. Drugs 2005; 65: 1317-36

120. Appelbaum PC, Jacobs MR. Recently approved and investigational antibiotics for treatment of severe infections caused by Gram-positive bacteria. Curr Opin Microbiol 2005; 8: 510-7

121. Labthavikul P, Petersen PJ, Bradford PA. In vitro activity of tigecycline against *Staphylococcus epidermidis* growing in an adherent-cell biofilm model. Antimicrob Agents Chemother 2003; 47: 3967-9

122. Yin LY, Lazzarini L, Li F, et al. Comparative evaluation of tigecycline and vancomycin, with and without rifampicin, in the treatment of methicillin-resistant *Staphylococcus aureus* experimental osteomyelitis in a rabbit model. J Antimicrob Chemother 2005; 55: 995-1002

123. Madsen D, Blais J, Park C, et al. In vitro profiling of the new carbacephem BP-102 [abstract]. 45th ICAAC, American Society for Microbiology; 2005 Dec 16-19; Washington, DC. 2005; F-1456

124. Craig WA, Andes DR, Dudley M, et al. In vivo activity of BP-102, a new carbacephem, against methicillin-susceptible and -resistant strains of *Staphylococcus aureus* (MSSA and MRSA) in the thighs of neutropenic mice [abstract]. 45th ICAAC, American Society for Microbiology; 2005 Dec 16-19; Washington, DC. 2005; F-1166

125. Trampuz A, Zimmerli W, Murphy CK, et al. Efficacy of novel rifamycin ABI-0043 against *Staphylococcus aureus* in a foreign-body infection model. 45th ICAAC, American Society for Microbiology; 2005 Dec 16-19; Washington, DC. 2005: LB-6

126. Rothstein DM, Mullin S, Sirokman K, et al. Novel rifamycin derivatives possess good in vivo efficacy in a rifamycin-resistant *Staphylococcus aureus* infection model [abstract]. 44th ICAAC, American Society for Microbiology; 2004 Oct 30-Nov 2; Washington, DC. 2004: F-365

127. Rothstein DM, Farquhar R, Sorokman K, et al. In vivo efficacy of novel rifamycin compounds against wild type and rifampin-resistant *Staphylococcus aureus* strains [abstract]. 45th ICAAC, American Society for Microbiology; 2005 Dec 16-19; Washington, DC. 2005: F-2045

128. Murphy CK, Mullin S, Osburne MS, et al. In vitro activity of novel rifamycins against rifamycin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2006; 50: 827-34

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