Antibiotics in Treatment of Periprosthetic Joint Infections

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Introduction

The infection rate after joint arthroplasty is about 1–3 % in spite of correct surgical techniques, aseptic measures, and antibiotic prophylaxis [1]. Taking into account the increasing number of arthroplasties performed each year in the developed world; a parallel increase in the number of prosthetic joint infections is expected. The management of these infections is complex due to the progressive increase in antibiotic resistant bacteria and the ability of bacteria to grow forming biofilms on the implant surface. The aim of the present chapter is to provide a general knowledge about antibacterial agents and the main characteristics of available antimicrobial families for treating the most frequent pathogens producing prosthetic joint infections. The description of each group of antibiotics includes the following aspects: mechanism of action, antibacterial spectrum, pharmacodynamic index predicting the efficacy, concentration achieved in bone, recommended dosages and way of administration, and the most relevant adverse events.

Bacteria, most especially *Staphylococcus aureus* have developed mechanisms to evade the immune system and to remain hidden but viable for a long period of time causing recurrent relapses. The most important mechanisms related with orthopedic implant infections are the ability to form biofilms [2] and the phenotypic switch to small colony variants (SCV) that are able to survive within osteoblasts [3, 4]. A summary of the data available about the activity of antibiotics against these bacteria is included in the description of each group of antibiotics.

General Concepts of Antibacterial Agents

Classically antibiotics have been divided in bactericidal or bacteriostatic and in general bactericidal agents are preferable to static ones, however, this distinction should not be taken as absolute. The definition of cidality is a laboratory concept. Bactericidal agents are those that kill bacteria rapidly (≥3 logarithms of colony forming units in 24 h) while bacteriostatic, also kill bacteria, but they do it slowly (Fig. 9.1). Bactericidal agents are preferred when host's defenses are insufficient like in neutropenic patients or when the infection is located in sites where neutrophil penetration is difficult like in meningitis or endocarditis. However, in other circumstances a bacteriostatic agent could be better. This is the case of necrotizing fasciitis due to *Clostridium perfringens* or *Streptococcus pyogenes* where animal models and some clinical data show that clindamycin or

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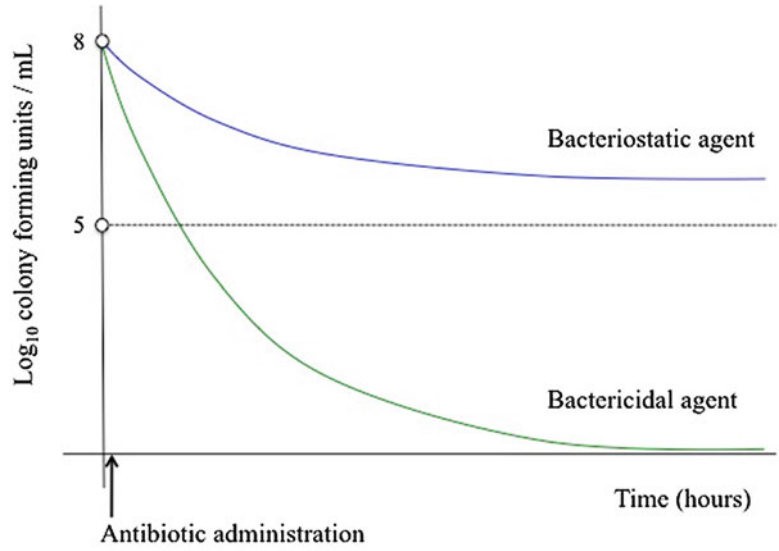

Fig. 9.1 Killing curve describing the activity of a bacteriostatic antibiotic (*blue*, reduction of <3 log of colony forming units after 24 h of exposure) and other bactericidal (*green*)

linezolid (static agents) prevent mortality better than betalactams (cidal agents). Protein synthesis inhibitors (clindamycin, linezolid, rifampin, tetracyclines) abruptly stop the production of toxins, critical in the pathogenesis of necrotizing fasciitis, while betalactams do not reduce or even increase the toxin production during the first 24 h [5].

The effectiveness of antibiotics depends on their in vitro activity well described by the minimum inhibitory concentration (MIC). The MIC is the minimal antibiotic concentration that inhibits the macroscopic growth of bacteria, therefore, the lower the MIC the higher the activity. Based on this information, microbiologist inform about the susceptibility or resistance of bacteria to each antibiotic. Although MIC is a useful tool for predicting the efficacy of antibiotics, experience from animal models and clinical studies has shown that the information provided by the MIC is limited. This test is performed in the laboratory using low bacterial inoculum in exponential growth phase and using static antibiotic concentrations while in patients, bacterial inoculum could be significantly higher and antibiotic concentration in serum and tissues is constantly changing. For this reason, during the last years infectious disease physicians, microbiologists, and pharmacologists have investigated in animal models and human beings the relationship between measurements of drug exposure (pharmacokinetics: absorption, distribution, and elimination) and antimicrobial effect (MIC), this interaction is called pharmacodynamics [6]. The development of pharmacodynamics has proven valuable for the design of appropriate regimens and to define more accurate susceptibility break points. It is possible to identify three patterns of antimicrobial activity (Fig. 9.2):

1. *Concentration-dependent antibiotics with prolonged post-antibiotic effect*. Higher serum concentration of these antibiotics kills microorganisms more rapidly than lower levels, and prolonged post-antibiotic effect allows for infrequent administration of large doses. The goal of a dosing regimen of these drugs would be to maximize concentrations over the MIC (Cmax/MIC). This pattern is observed with aminoglycosides.
2. *Time-dependent antibiotics with minimal or no post-antibiotic effects*. High antibiotic concentrations do not kill microorganisms better than lower levels and microorganisms regrowth very soon after serum levels fell below the MIC. This pattern is typical of

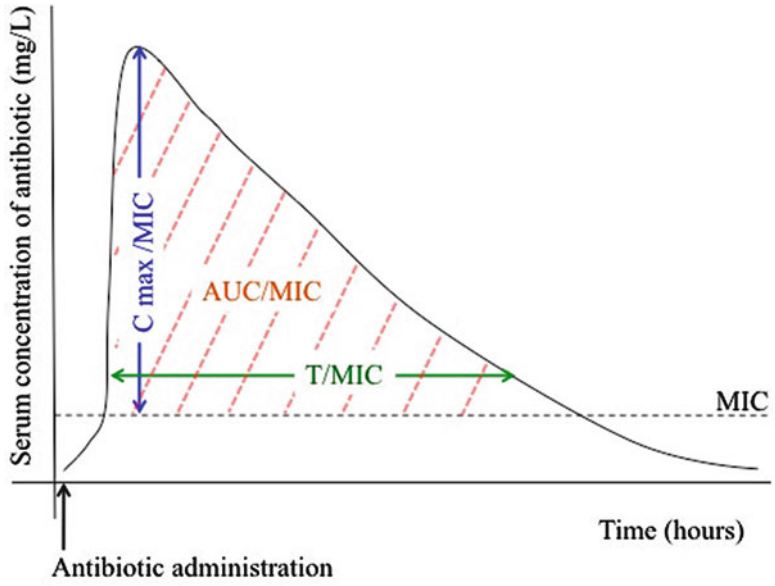

Fig. 9.2 Description of pharmakodynamic parameters predicting the antibiotic efficacy. *Cmax* peak serum antibiotic concentration, *MIC* minimum inhibitory concentration, *AUC* area under the concentration curve

betalactams and the goal of a dosing regimen is to maintain serum levels over the MIC for the entire period between two doses (T > MIC).

3. *Global exposure-dependent antibiotics*. These antibiotics are time-dependent with prolonged post-antibiotic effects preventing regrowth during the interval the serum concentration is below the MIC or concentration-dependent antibiotics with prolonged half-life. The goal of a dosing regimen is to optimize the amount of drug to ensure that killing occurs and the best parameter describing the global exposure is the area under the concentration curve for 24 h/MIC (AUC/MIC). This pattern is observed in the majority of antibiotics not included in the previous two groups: macrolides, clindamycin, metronidazol, glycopeptides, oxazolidinones, fluoroquinolones, daptomycin, or tetracyclines.

Significance of Antimicrobial Concentrations in Bone, Synovial Fluid, and Abscess

The majority of bacterial infections occur in the interstitial fluid of tissues (bone) or in other body fluids (synovial fluid); therefore, penetration into the extravascular space is highly important for antimicrobial therapy. Systemically administered antibiotics enter vascular circulation and diffuse (soft-tissue, skeletal muscle, bone, synovial fluid) or are secrete (urine, bile) into different human body sites. The concentrations achieved in these sites is the result of serum drug concentration, protein binding, half-life, lipid solubility, ionization, active transport, extravascular site geometric (big or small joints), and degree of inflammation. The extravascular sites of antibiotic distribution may be divided in four major categories that are described in Table 9.1.

Table 9.1 Categories of extravascular sites that have been evaluated for antibiotic distribution

Site description	Examples
Whole-body tissues	Skeletal muscle, skin, bone
Fluid-filled spaces of relatively large volume into which drug passively diffuses	Synovial fluid, abscesses, bursae, blisters
Fluid produced by the excretion or secretion of glands or organs	Urine, bile, sputum, saliva, sweat
Fluid-filled spaces with probable diffusion barriers or active excretory systems	Cerebrospinal fluid, vitreous humor

Over the last decades, several studies have been published on antibiotic penetration into bone [7]. Bone is a less vascularized tissue than, for example, the lungs or skin and it has a particular composition making difficult to predict whether agents showing good penetration into other tissues will also achieve high concentrations in bone. Bone tissue consists of an organic fraction (30–35 % of total bone mass, collagen fibrils, and extracellular fluid) and an inorganic fraction (65–70 %, hydroxyapatite crystals). In acute hematogenous osteomyelitis the microorganisn seed in the interstitial fluid (organic fraction) while in contiguous infections (diabetic foot or surgical infection) the microorganism colonize the inorganic and organic matrix. Since antibiotic concentration achieve in extracellular fluid is similar to that in serum [8], acute hematogenous osteomyelitis, without sequestrum or abscess, can be treated successfully with systemic antibiotics [9]. In contrast, inorganic matrix is poorly vascularized, antibiotic concentration is low and, therefore, contiguous infections frequently need surgical intervention to cure. According to this data, it would be desirable to identify the antibiotic concentration in the different bone compartments, however, techniques to separate a bone sample into, for example, extracellular fluid, collagen fibrils, bone cells, and hydroxyapatite are not available and virtually all published studies measure the total drug concentration in a bone homogenate (mix of organic and inorganic compartments). During the last years, the authors have made an effort to analyze separately cancellous bone, the inner part of the long bones that contains a higher proportion of extravascular fluid and a lower percentage of inorganic matter and cortical bone with a higher percentage of inorganic matter [7], and new techniques like microdialysis have been developed to measure the unbound (free) drug in the interstitial fluid of tissues. The majority of the articles describe the bone penetration as the ratio between bone and serum concentration, a review of the most relevant data available is provided in each antibiotic description.

Synovial fluid is produced by synovial membrane; this membrane is composed of vascularized connective tissue surrounded by a cuboidal

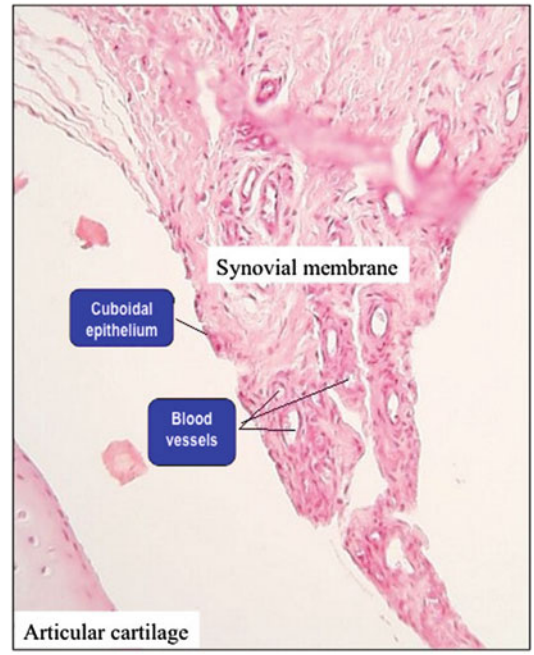

Fig. 9.3 A detail of the synovial fluid structure

epithelium that lacks a basement membrane (Fig. 9.3). Therefore, there are no barriers for antibiotic diffusion to synovial fluid as it is described in Table 9.2. However, the majority of these data were performed in subjects who underwent a joint surgery and not in patients with septic arthritis. In septic arthritis the volume of joint space is significantly higher than in non-septic arthritis. The ratio between interchangeable surface (synovial membrane) and volume of joint space determines the time needed to achieve the equilibrium between serum and synovial fluid (see below the details for antibiotic diffusion to abscess). It explains the need for immediate synovial fluid drainage in case of septic arthritis.

Abscess formation starts with the attraction of polymorphonuclear leukocytes that degrades infected tissue generating liquefaction necroses. Granulation tissue subsequently develops at the abscess border that is finally replaced by a fibrous capsule (Fig. 9.4). Animal model data suggested that the encapsulation phase occurs 10–14 days following infection. Permeability to antibiotics of the abscess wall varies depending on the stage of encapsulation. Three main factors determining

Table 9.2 Concentration of different antibiotics in synovial fluid

Antibiotic	Number of patients	Time from infusion (h)	Concentration in synovial fluid (μg/mL)	Ratio synovial fluid/ serum concentration
Gentamycin	6	1–3.5	3.2	80
Cefotaxime	22	2	29	116
Cloxacillin	29	0.75	105	87
Vancomycin	6	1–1.65	5.7	81
Linezolid	10	1.5	20.1	87

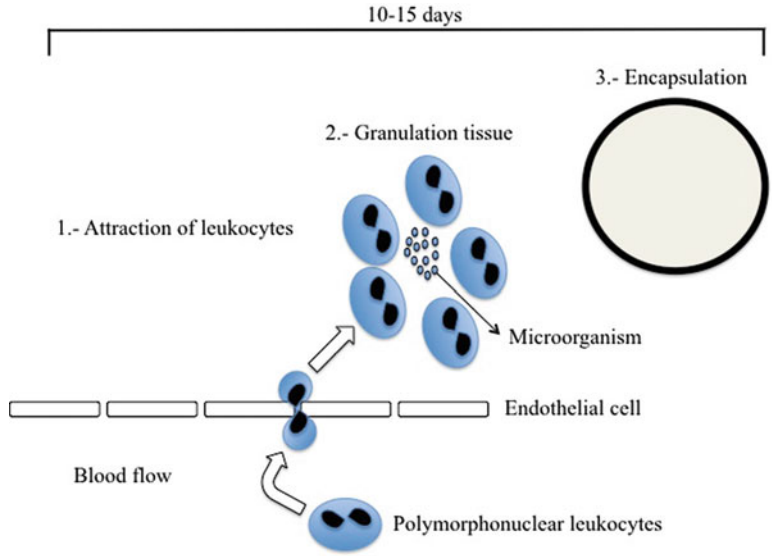

Fig. 9.4 Phases of abscess formation

the antibiotic concentration into abscess and the time needed to achieve the equilibrium between plasma and abscess are:

1. The permeability of the capsule that decreases in the course of abscess formation. Permeation is defined as the passive migration of a solute through a solid membrane and it is higher for low molecular weight, high lipid solubility, and non-dissociated antibiotics. This parameter is very difficult to evaluate in human beings and probably is the main reason to explain the variability reported by different authors.
2. The ratio between surface (A) and the total volume (V) of abscess. Equilibrium between plasma and abscess concentration is delayed in abscess with a low A/V ratio, as a drug enters and leaves more slowly.
3. Gradient of concentration between plasma and abscess. Higher free serum (unbound to proteins) antibiotic concentrations are necessary to obtain high antibiotic concentrations into abscesses.

Information about antibiotic diffusion to abscesses in human beings is scarce and some of the most relevant information is shown in Table 9.3. In addition, other factors like low oxygen availability, low pH of abscess fluid, and high bacterial inoculum determine a significant reduction in the efficacy of antibiotics against bacteria in abscesses. According to clinical data, success treating abscess without surgical drainage is strongly associated with an abscess size <5 cm and prolonged (>4 weeks) duration of antibiotics [10].

Table 9.3 Antibiotic levels measured in human abscess fluid

Antibiotic	Dose and interval	Doses until drainage	Plasma concentration (μg/mL)	Abscess concentration (μg/mL)
Cefotaxime	3 g/8 h i.v.	1–7	Conc. after 6 h of the last dose = 2 ± 1	Conc. after 6 h of the last dose = 2.1 ± 1.6
Amoxicillin	500 mg p.o.	1	Conc. after 1.5 h = 5.92 ± 2	Conc. after 1.5 h = 0.9 ± 0.3
Fosfomycin	8 g i.v.	1	Conc. max. (0.8 h) = 446 ± 128	Conc. max. (10.5 h) = 64.2 ± 66.9

Classification of Antibiotics and Principal Mechanisms of Resistance

For the present chapter, antibiotics are grouped according to the main mechanism of action:

1. Cell wall active antibiotics: betalactams and glycopeptides.
2. Antibiotics causing cytoplasmic membrane disruption: daptomycin.
3. Inhibitors of protein and RNA-synthesis machinery: aminoglycosides, clindamycin, tetracyclines, rifampin, and linezolid.
4. Inhibitors of folic acid synthesis: cotrimoxazole.
5. Inhibitors of the specific enzymes involved in DNA synthesis and supercoiling: fluoroquinolones.

Bacteria have developed mechanisms to circumvent the action of antibiotics. These mechanisms could be grouped in: (1) Antibiotic modification by breaking down the molecule using enzymes. For instance, betalactamases hydrolyze the betalactam ring of penicilins and are responsible of high penicillin-resistant in *S. aureus* (>90 %). (2) Modification of the target site preventing the binding of the antibiotic. An example is the acquisition of a protein binding penicillin (PBP) with a mutation in the betalactam binding site that makes *S. aureus* resistant to all betalactams including those resistant to the action of betalactamases like methicillin (MRSA). (3) Prevention of access to the target by inhibiting uptake. This mechanism is important for Gram-negatives since these bacteria have an outer membrane that has porins, which permit only the entry of small (≤700 Da) hydrophilic antibiotics. By loosening these pores, bacteria become resistant to those antibiotics that use this channel. (4) Prevention of access to the target site by increasing export of the drug using efflux pumps. These pumps have been described in Gram-positive and Gram-negative bacteria and are responsible for resistance to fluoroquinolones or tetracyclines.

Cell Wall Active Antibiotics

Betalactams

Betalactams block the transpetidase activity of PBP. These antibiotics are bactericidal and time-dependent. The maximum effect is obtained when free serum concentrations are fourfold the MIC for at least 40 % for carbapenems, 50 % for penicillins, and 60 % for cephalosporins of the interval between two consecutive doses (T>MIC). However, in severe infections the clinical evidence suggests that the maximum effect is achieved when the serum concentration of the betalactam is 100 % over the MIC. The antimicrobial spectrum of the main groups of betalactams including penicillins, cephalosporins, and carbapenems is shown in Table 9.4. The most active drugs against betalactam susceptible *S. aureus* are the penicillins resistant to the penicillase (methicillin, oxacillin, or flucloxacillin) followed by cefazolin that is widely used for treatment and prophylaxis. However, *S. aureus* produces four different types of penicillases (A, B, C, and D) and those producing type A are less susceptible to cefazolin. This fact has been associated with prophylaxis [11] and treatment [12] failure most especially in acute infections with high bacterial inoculum and when it is not planned to remove the implant. The recommended

Table 9.4 Description of antimicrobial spectrum of betalactams

Group	Antibiotic/s	Route	Predominant activity
Penicillins			
Naturals	Penicillin G	im-iv	GP
	Penicillin V	Oral	
Resistant to penicillase	Methicillin	im-iv	*S. aureus*
	Oxacillin	im-iv	
	(Flu) Cloxacillin	im-iv-oral	
Aminopenicillins	Ampicillin	im-iv-oral	GP, *Enterococcus faecalis*
	Amoxicillin	Oral	
	Combinations with clavulanic acid or sulbactam	im-iv-oral	GP, *E. faecalis*, GN, anaerobes
Carboxi and ureidopenicillins	Piperacillin-tazobactam	im-iv	GN, *Pseudomonas aeruginosa*, *E. faecalis*, anaerobes
Cephalosporins			
First generation	Cefazolin	im-iv	GP
	Cefalexin	Oral	GP
Second generation	(Axetil-) Cefuroxim	im-iv-oral	GP, GN
	Cefonicid[a]	im-iv	GP, GN
	Cefoxitin	im-iv	GP, GN, anaerobes
Third and fourth generation	Ceftriaxone[a]	im-iv	GN
	Ceftazidime	im-iv	GN, *P. aeruginosa*
	Cefepime	im-iv	GN, *P. aeruginosa*
Fifth generation	Ceftaroline[b]	iv	GN, GP, active against MRSA
Carbapenems			
Activity against *Pseudomonas aeruginosa*	Imipenem	iv	GP, GN, *P. aeruginosa*, ESBL-E, anaerobes
	Meropenem[c]	iv	
	Doripenem[c]	iv	
Without activity against *P. aeruginosa*	Ertapenem	iv	Idem, without activity for *P. aeruginosa*

GP Gram-positive (excluding methicillin-resistant staphylococci and *Enterococcus* spp.). *GN* Gram-negative (excluding *Pseudomonas* spp. and ESBL-E), *ESBL-E Enterobacteriaceae* (*Escherichia*, *Klebsiella*) producing extended spectrum betalactamases, *MRSA* methicillin-resistant *Staphylococcus aureus*

[a]Antibiotics with long half-life

[b]The first betalactam with activity against MRSA

[c]Meropenem and Doripenem are more active than Imipenem for *P. aeruginosa*

dosages and way of administration for a selection of betalactams is shown in Table 9.5. The majority of betalactams has a short half-life and should be administered several times per day or in continuous infusion [13, 14] to achieve the pharmacodynamic index (T>MIC). The majority of studies of betalactams and betalactamase inhibitors (clavulanic acid, tazobactam, sulbactam) have reported a bone concentration of 10–30 % of the serum concentration and the rate of equilibration between bone and serum is relatively fast but penetration into cortical bone is low [7].

The activity of betalactams against Gram-positive or Gram-negative biofilms is limited. The activity of penicillins (penicillin and oxacillin), cephalosporins (cefazolin), and carbapenems (imipenem) against planktonic and biofilm of *S. aureus* and *P. aeruginosa* have been studied in the laboratory [15, 16]. The concentration needed to eradicate biofilms was in general more than 100-fold higher than the concentration needed for planktonic populations. The efficacy against SCV is limited most especially against intracellular cells [17]. Probably the lack of efficacy of betalactams is due to the low metabolic activity of bacteria in biofilms and SCV. These data suggest that betalactams are good drugs for acute infection due to susceptible Gram-positives

Table 9.5 Dose, route, and way of administration of the main betalactams

Antibiotic	Dose	Frequency	Route	Main coverage
(Flu) Cloxacillin	2 g	4 h	iv	MSSA
	LD: 0.5–1 g (10–30 min) +			
	CI 8–12 g	In 24 h	iv	
Cefazolin	1–2 g	8 h	iv	MSSA
	LD: 0.5–1 g (10–30 min) +			
	CI: 60–80 mg/kg	In 24 h	iv	
Ampicillin	2 g	4 h	iv	*E. faecalis*
Amoxicillin-clavulanate	875/125 mg	8 h	Oral	MSSA, GN, anaerobes
	1–2 g	8–6 h	iv	
Piperacillin-tazobactam	3/0.375 g	6 h	iv	*P. aeruginosa*
Ceftriaxone	1–2 g	24 h	iv	GN
Ceftazidime	2 g	8 h	iv	*P. aeruginosa*
	LD: 0.5–1 g (10–30 min) +			
	CI 6 g	In 24 h	iv	
Meropenem	1–2 g (first 500 mg in 10–30 min) infuse in 2–3 h (preferable)	8 h	iv	*P. aeruginosa* ESBL-E
Ertapenem	1 g	24 h	iv	ESBL-E

LD loading dose, *CI* continuous infusion, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *GN* Gram-negatives (excluding *Pseudomonas* spp. and ESBL-E), *ESBL-E* extended spectrum betalactamase *Enteroacteriaceae* (*E. coli*, *K. pneumoniae*,…)

or Gram-negatives where the rapidly growing bacteria is the dominant bacterial population but their efficacy is limited for eradicating biofilms and, therefore, other alternatives for long-term therapy would be preferable.

The most relevant adverse events are immediate allergic reactions mediated by IgE (angioneurotic edema, broncospasm, hypotension, urticaria) documented only in 0.01 % of the patients receiving penicillin derivatives. Late allergic reactions mediated by IgG are more frequent and characterized by skin rash. Ten percent of patients with penicillin allergy are also allergic to cephalosporins, therefore, are not recommended at least for those patients with antecedents of immediate reactions. Gastrointestinal alterations associated with oral betalactams like nausea, vomiting, and nonspecific diarrhea or *Clostridium difficile*-associated diarrhea. In patients receiving more than 10 days of treatment at dosages higher than 150 mg/kg/day neutropenia is a potential hematological adverse event. Betalactams, especially imipenem or cefepime at high dosages and in patients with renal failure, are associated with risk of convulsion.

Glycopeptides: Vancomycin

Vancomycin binds to D-Alanin-D-Alanine terminal residues of the monomeric component of peptidoglycan inhibiting the cell wall synthesis. Vancomycin is a time-dependent antibiotic with a slower bactericidal activity. This could explain clinical data showing that patients with osteomyelitis due to methicillin-susceptible *Staphylococcus aureus* (MSSA) treated with vancomycin had a worse outcome than those treated with betalactams [18], therefore, when vancomycin is selected as a first-line therapy but MSSA is finally the etiology of the infection, it would be better to switch therapy to a betalactam. From animal models and clinical experience in respiratory tract infections and bacteremia due to MRSA [19, 20], we have learnt that the best predictor of vancomycin efficacy is the AUC/MIC and the outcome is significantly better when this ratio is ≥400. Recent consensus recommends a trough vancomycin serum concentration ≥15 mg/L [21]. The dosage required for obtaining this target when the MIC of vancomycin is ≤1 mg/L is shown in Table 9.6. Clinical experience using vancomycin in patients

Table 9.6 Dose, route, way of administration and main coverage of different antibiotics

Antibiotic	Dose and frequency	Route	Main coverage
Vancomycin	15–20 mg/kg/12 h[a]	iv	MRSA MRCNS *E. faecium*
Daptomycin	6–10 mg/kg/24 h[a, b]	iv	MRSA MRCNS *E. faecium*
Aminoglycosides			
Gentamycin	5–7 mg/kg/24–12 h[a]	iv, im	GP, GN
Amikacin	15–20 mg/kg/24–12 h[a]	iv, im	GP, GN, *P. aeruginosa*
Clindamycin	300 mg/8 h 600 mg/8–6 h CI: 30–40 mg/kg in 24 h	Oral iv iv	GP, anaerobes
Tetracyclines[c]			
Doxicycline	200 mg (1 dose) 100 mg/12 h	iv, oral	GP, GN, anaerobes
Minocycline	200 mg (1 dose) 100 mg/12 h	iv, oral	GP, MRSA, GN, anaerobes
Tigecycline	100 mg (1 dose) 50 mg/12 h	iv	GP, MRSA, *Enterococcus* spp., GN, anaerobes
Rifampin	450–900 mg/24–12 h	iv, oral	GP, MRSA
Linezolid	600 mg/12 h	iv, oral	GP, MRSA, *Enterococcus* spp.
Cotrimoxazole (sulfamethoxazole/trimethoprim)	160/800 mg/12–8 h	iv, oral	MRSA
Fluoroquinolones			
Ciprofloxacin	400 mg/12–8 h 750 mg/12 h	iv, oral	GN, *P. aeruginosa*, GP
Levofloxacin	500 mg/24–12 h	iv, oral	GN, *P. aeruginosa*, GP
Moxifloxacin	400 mg/24 h	iv, oral	GN, GP, anaerobes

MRSA methicillin-resistant *S. aureus*, *MRCNS* methicillin-resistant coagulase-negative staphylococci, *GN* Gram-negatives (excluding *Pseudomonas* spp.), *GP* Gram-positives (excluding methicillin-resistant staphylococci and *Enterococcus* spp.), *CI* continuous infusion

[a]According to total body weight

[b]Doses higher than 6 mg/kg are recommended for severe infections and when the implant is not removed. In morbid obese patients do not give doses higher than 8 mg/Kg

[c]Minocycline and tigecycline are more active against *S. aureus* than doxicycline

with bacteremia due to staphylococci with a vancomycin MIC > 1 mg/L showed a higher failure and mortality rate [22]. Although there is no clinical experience in bone and joint infections, it is prudent to select an alternative anti-staphylococcal agent when vancomycin MIC > 1 mg/L.

In hip replacement patients, mean concentration of 7 % of the serum concentration has been reported in cortical bone and 13 % in cancellous bone, and only three of six bone samples from osteomyelitis patients had concentrations above the lower limit of detection [23]. The activity of vancomycin against biofilms, extra- and intracellular SCV in vitro as well as in animal models is very limited [15, 17]; however, biofilm activity improves when combining with rifampin or tetracyclines [24].

The most important adverse events are phlebitis (10 %), red-man syndrome during rapid intravenous infusion characterized by itching, skin rash, and nephrotoxicity. Red-man syndrome is avoided by slow infusion (1 h). Nephrotoxicity is associated with a trough serum concentration >15 mg/L, duration longer than 7 days or

concomitant nephrotoxic drugs (diuretics, aminoglycosides, anfotericin B) and in these situations is higher than 20 %.

Antibiotics Causing Cytoplasmic Membrane Disruption: Daptomycin

Daptomycin is a lipopeptide with a potent concentration-dependent bactericidal activity against Gram-positive cocci. The large hydrophobic cluster of the lipopeptide interacts with the acyl chain region of the bacterial membrane. Once inserted into the membrane, molecules of daptomycin form pores that disrupt the functional integrity of the cytoplasmic membrane allowing the release of intracellular ions and rapid cell death [25]. The pharmacodynamic index that predicts the efficacy of daptomycin is the AUC/MIC and the target value is ≥600. Although accepted doses (4–6 mg/kg/24 h intravenously) achieve high AUCs, clinical experience in patients with osteomyelitis or prosthetic joint infections demonstrated that low doses (4 mg/kg/24 h) were associated with significantly worse outcomes than higher doses [26, 27]. A recent open, randomized clinical trial in patients with a prosthetic joint infection due to staphylococci who underwent a 2-stage exchange were randomized to receive daptomycin 6 or 8 mg/kg or the comparator (vancomycin in the majority of the cases) for 6 weeks [28]. The clinical success rate was similar in the three groups, 88 %, 91 %, and 91 %, respectively. Considering also adverse events and microbiological failure, the success rates were 58 %, 61 %, and 38 %, respectively. These results suggest that for bone infections doses higher than 6 mg/kg are necessary (Table 9.6), probably because this antibiotic is highly protein bounded (92 %) and it has a large molecular weight. In poor vascularized areas where the interchangeable surface is small compared with the volume of infected tissue (i.e., devitalized tissue surrounding prosthesis, undrained abscesses) the promptness to achieve the desired tissue concentration of any drug depends on the speed of molecular diffusion. The speed of molecular diffusion depends, in turn, on the concentration gradient of free drug between capillaries and the center of the lesion and the physical and chemical properties of the molecule. Obtaining a high drug-free concentration gradient (high dose) allows to rapidly achieve, in the infectious foci, a concentration higher than the MIC. In addition, animal models have shown that results are better when combining daptomycin with rifampin [29, 30].

Daptomycin cancellous bone concentrations were measured in eight diabetic patients using microdialysis [31]. Results showed that free plasma daptomycin concentration is equal to free bone concentration. According to in vitro data, daptomycin is one of the most potent antibiotics against biofilms [32], probably because the bactericidal activity of daptomycin is less affected by cell division or active metabolism [33]. Daptomycin is bactericidal against extracellular SCV at fourfold daptomycin MIC [34] but the activity against intracellular SCV is significantly reduce and only partially recovered when combining with rifampin and gentamycin [35].

The most important adverse event is a toxic myopathy that in general appears after 2 weeks of therapy and at high doses. According to different studies, using a mean dose of 8 mg/kg, 10 % of patients develop an increase of creatine phosphokinase (CPK) and 4–5 % symptoms of myopathy. It is recommended to stop daptomycin when there are clinical symptoms of myopathy or CPK levels ≥5 times the normal values.

Inhibitors of Protein and RNA-Synthesis Machinery

Aminoglycosides

Aminoglycosides bind to prokaryote ribosomes resulting in a measurable decrease in protein synthesis. The majority of antibiotics with a similar mechanism of action (tetracyclines, clindamycin, linezolid) are bacteriostatic; however, aminoglycosides are rapid bactericidal and concentration-dependent antibiotics. This suggests additional unidentified mechanisms of bactericidal activity.

Aminoglycosides are transported across the cytoplasmic membrane by an energy-dependent mechanism that is inhibited in low pH and anaerobic conditions that explain the reduced activity of these antibiotics against anaerobes and bacteria in abscesses. The spectrum of aminoglycosides includes aerobic and facultative Gram-negative bacilli (*Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter* spp.) and Gram-positives. MSSA remain susceptible but MRSA are frequently resistant. Streptococci and enterococci are resistant to aminoglycosides. In general, these antibiotics show synergy when combined with cell wall-active antibiotics (betalactams and vancomycin). Although the half-life of aminoglycosides is short, the rate of bacterial killing increases as the antibiotic concentration is increased (Cmax/MIC) and they have a prolonged post-antibiotic effect, therefore, the optimal regimen is a high dose once or twice daily (Table 9.6). The information about bone penetration of aminoglycosides is scarce. The activity against biofilms is limited since they are cationic molecules and extracellular matrix of biofilms contains anionic polysaccharides that probably do not allow aminoglycoside diffusion [32]. SCV are highly resistant to these antibiotics because the energy-dependent transport is blocked in SCV and aminoglycoside is not internalized [36]. In addition, a retrospective study of 50 episodes of enterococcal prosthetic joint infections analyzed the outcome among those receiving monotherapy (cell wall-active antibiotic) versus combination therapy with an aminoglycoside [37]. Groups did not differ with respect to outcome but nephrotoxicity and ototoxicity was higher in the aminoglycoside group. According to this information, the use of aminoglycosides is restricted to acute phase of severe infections in combination with cell wall-active antibiotics, for no longer than 3–5 days and for the treatment of multidrug-resistant Gram-negatives like *P. aeruginosa*.

The reported incidence of nephrotoxicity varies from 5 to 25 % range but concomitant use of other nephrotoxic drugs (diuretics, vancomycin), preexisting renal diseases, and >3 days of treatment have been significantly associated with a higher risk. It is recommended to measure peak and through serum levels to guarantee their efficacy and avoid toxicity. Other serious adverse events are ototoxicity and neuromuscular blockade.

Clindamycin

Clindamycin binds to 50S ribosomal subunit and blocks the protein synthesis in early chain elongation by interference with the transpeptidation reaction. The activity includes Gram-positives and anaerobes. It is important to mention that some Gram-positives (staphylococci) have inducible resistance to clindamycin. This mechanism of resistance is not captured by the standard MIC but there are reports showing clinical failure to clindamycin in patients with infections due to staphylococci with inducible resistance [38]. This mechanism of resistance should be suspected when a clindamycin-susceptible strain is resistant to erythromycin. In these cases, before giving clindamycin, it is necessary to apply for an additional test to rule out inducible resistance. Clindamycin is a time-dependent and bacteriostatic antibiotic and the recommended doses are shown in Table 9.6. Like other protein synthesis inhibitors, clindamycin rapidly reduces the synthesis of virulence factors that are critical in the pathogenesis of infection [5]. Studies of clindamycin bone penetration in humans were conducted in 1970s and the range of bone:serum ratio was 0.20–0.45, therefore, slightly higher than betalactams. Indeed, animal models of osteomyelitis showed that clindamycin was superior to cefazolin in the eradication of *S. aureus* from infected bone [39]. Combined with rifampin, clindamycin has shown a high success rate in short series of orthopedic implant infections [40]. Zeller et al. [41] described that patients treated concomitantly with rifampicin compared to patients with clindamycin monotherapy had a 40 % decrease in clindamycin serum concentration; however, they did not find differences in the clinical outcome.

The most important adverse events are gastrointestinal disturbances including diarrhea, nausea, vomiting, and abdominal pain that have been

reported in 10 % of the cases. Diarrhea associated with *Clostridium difficile* is a severe complication reported in <5 % of cases.

Tetracyclines

Tetracyclines inhibit bacterial protein synthesis by binding the 30S ribosomal subunit and are broad-spectrum, bacteriostatic, and time-dependent (T>MIC) antibiotics active against Gram-positive and Gram-negative bacteria. Since the 1970s the identification of an increasing number of tetracycline-resistant pathogens has limited their usefulness in clinical practice. Recently, a new generation of tetracyclines (tigecycline) that retains the broad spectrum of activity has been developed. The dosage of the main tetracyclines is shown in Table 9.6.

Modern analytical techniques for measuring bone concentrations of tigecycline have demonstrated a high bone penetration [7]. In vitro studies have shown that tetracyclins are active antibiotics against staphylococcal biofilms [42], most especially in combination with other antibiotic including rifampin, clindamycin, or vancomycin [24] and against intracellular SCV [17]. An animal model of chronic foreign-body infection due to MRSA demonstrated similar results for tigecyclin and vancomycin and both were significantly better than control [43]. Clinical experience in prosthetic joint infections is limited to the use of minocycline as suppressive therapy for a prolong period [44]. Tolerance was excellent and no relapse was observed in 50 % of cases at the last follow-up.

Gastrointestinal symptoms (nausea, vomiting) are common after oral administration of tetracyclines. The administration of food with doxycycline or minocycline may ameliorate some of these symptoms. A gray-brown to yellow discoloration of the teeth has been noted in children taking tetracyclines. The administration of less than 2 g/day IV is not associated with liver dysfunction or injury except in pregnant women. The tetracyclines aggravate preexisting renal failure. Hypersensitivity reactions, including anaphylaxis, urticaria, periorbital edema, fixed drug eruptions, and morbilliform rashes, and photosensitivity reactions are not common. Vertigo, a side effect unique to minocycline that usually begins on the second or third day of therapy, has been noted more frequently in women. The symptoms are reversible within several days after discontinuation of therapy, but this side effect has seriously limited the use of minocycline. Benign intracranial hypertension (pseudotumor cerebri) has been described in general associated with the medium- or long-term use of minocycline.

Rifampin

Rifampin exerts their antimicrobial activity by inhibiting the β-subunit of DNA-dependent RNA polymerase, which is highly conserved among prokaryotic organisms. Rifampin is a bactericidal and concentration-dependent (Cmax/MIC) antibiotic with potent activity against Gram-positives and mycobacteria. Rifampin maintains activity against bacteria in stationary phase [45], intracellular SCV, [17] and bacteria in biofilms [32]. The recommended doses are shown in Table 9.6; however, it is important to note that rifampin should never be administered in monotherapy since the selection of resistant mutants is common. Rifampin at 450 mg/12 h combined with ciprofloxacin was more effective than ciprofloxacin alone (curing percentages of 100 and 53 %) in orthopedic implant infections treated without removing the implant [46]. Since rifampin is a concentration-dependent antibiotic (Cmax/MIC) once daily administration (600–900 mg/24 h) is easier and also allows a higher Cmax/MIC than the 450 mg/12 h dosage. In addition, taking into account the long duplicative rate of biofilm bacteria, the administration of rifampin once a day could be sufficient. Bone serum concentration ratios of about 0.2–0.5 have been reported for rifampicin [7]. Many observational studies have demonstrated the efficacy of rifampin combinations (fluoroquinolones, linezolid, cotrimoxazole, tetracyclines) in prosthetic joint infections [47, 48]. Rifampin reduces the serum concentration of other antibiotics (linezolid, cotrimoxazole, or clindamycin), anticoagulants (acenocumarol), or

antiepileptic drugs (phenytoin); therefore, close clinical control is mandatory.

Gastrointestinal symptoms, such as abdominal pain or cramping, nausea, vomiting, and diarrhea, are relatively common. Elevations of serum hepatic transaminase levels can occur during therapy but the incidence is relatively low (1 %), being higher among individuals with chronic liver disease, alcohol abuse, or co-administration of other potentially hepatotoxic medications. Skin rash and other skin reactions are common reasons for discontinuation; however, antihistamines or desensitization therapy has allowed continuation of rifampin therapy in some patients. Mild thrombocytopenia, leukopenia, and granulocytopenia are relatively common during rifampin therapy. Acute renal failure has been described with highly intermittent dosing regimens or on reinstitution of rifampin after a drug-free interval.

Linezolid

Linezolid inhibits the protein synthesis by binding to the 50S ribosome at its interface with the 30S unit, thereby preventing the formation of the 70S initiation complex. Linezolid is a bacteriostatic and time-dependent (T>MIC) antibiotic with activity against the majority of clinically important Gram-positive organisms, including *S. aureus* (methicillin-susceptible and methicillin-resistant strains), coagulase-negative staphylococci, *E. faecium*, and *E. faecalis* (vancomycin-susceptible and vancomycin-resistant strains). The recommended doses are shown in Table 9.6. The reported mean bone:plasma concentration ratios were between 0.2 and 0.5 for linezolid [7]. Its oral formulation and activity against methicillin-resistant staphylococci makes this antibiotic an attractive alternative to intravenous glycopeptides. A review of the literature shows a high success rate with linezolid (85–90 %) in orthopedic implant infections when implant was removed [49–55]. The success rate when the implant was not removed varied from 72 % in acute to 43 % in chronic infections [53, 56].

The most important adverse events are nausea, vomiting, and diarrhea. Thrombocytopenia and anemia are frequent when treatment is longer than 2 weeks; however, these adverse events are less frequent when combined with rifampin. The reason for this fact is that rifampin reduces serum linezolid concentration. Peripheral neuropathy has been described in patients receiving linezolid courses longer than 3 months. Lactic acidosis is an uncommon adverse event. Linezolid produces a weak inhibition of monoaminoxidase and potentiates the action of serotoninergic drugs.

Inhibitors of Folic Acid Synthesis: Cotrimoxazole

Cotrimoxazole is the combination of sulfamethoxazole and trimethoprim. Each one inhibits a different enzyme in the bacterial process of thymidin biosynthesis. Cotrimoxazole proved to be bactericidal and more than 90 % of *S. aureus* (including MRSA) are susceptible and it is also active against Gram-negatives different from *P. aeruginosa*. It has a high oral bioavailability that makes this drug an attractive option for the treatment of prosthetic joint infections according to the doses shown in Table 9.6. However, it has been documented that pus inhibited sulfonamides. A major component of pus is polymerized DNA, released from inflammatory cells and injured tissues. *S. aureus* is able to obtain thymidine from DNA and this thymidine antagonizes the antistaphylococcal effects of both trimethoprim and sulfamethoxazole. Therefore, it is recommended to start cotrimoxazole after debridement of all necrotic tissue and pus and preferentially in combination [57, 58]. Information about activity of cotrimoxazole against biofilms is scarce, but several in vitro data showed that SCV are resistant to cotrimoxazole. The most important adverse events associated with sulfonamides are allergic reactions with skin rash, fever, serum sickness-like syndrome, or hepatic necrosis. Interstitial nephritis and tubular necrosis are rare events. More serious adverse reactions caused by sulfonamides may include acute hemolytic anemia

sometimes related to a deficiency in erythrocyte glucose-6-phosphate dehydrogenase (G6PD), aplastic anemia, agranulocytosis, thrombocytopenia, and leukopenia. It is recommended to avoid the combination with oral anticoagulants. In general, it is a well-tolerated drug and it has been used in chronic prosthetic joint infections as a suppressive therapy.

Inhibitors of the Specific Enzymes Involved in DNA Synthesis and Supercoiling: Fluoroquinolones

Fluoroquinolones inhibit bacterial DNA-gyrase (topoisomerase II) and topoisomerase IV. These antibiotics have a potent concentration-dependent bactericidal activity against Gram-negatives and Gram-positives. The pharmacodynamic index that predicts their efficacy is the AUC/MIC and the optimal value is ≥125; however, according to in vitro data a ratio of 250 is necessary to avoid the selection of resistant mutants. This target is achieved using the higher doses recommended in Table 9.6. The higher doses are especially recommended during the first 5–7 days of treatment and for treating infections due to *Pseudomonas aeruginosa*. The most active fluoroquinolones against Gram-negatives including *P. aeruginosa* are ciprofloxacin and levofloxacin. The experience in orthopedic implant infections due to Gram-negatives is scarce but in general is considered that the outcome is poor. However, recent experience suggests that when fluoroquinolones (ciprofloxacin or levofloxacin) are included in the antibiotic regimen (combined with a betalactam for the first 14 days) the success rate is higher [59]. Fluoroquinolones are probably efficacious for the treatment of implant infections and osteomyelitis due to Gram-negatives for two reasons: (1) their diffusion to synovial fluid and bone [60] and (2) their activity against biofilms. In an in vitro model of a *Pseudomonas* biofilm, Tanaka et al. [16] showed that the bactericidal action of betalactams against biofilm cells was affected by the low rate of cell growth inside the biofilm, while that of fluoroquinolones was considerably greater and independent of the growth rate. Unfortunately, the resistance rate to fluoroquinolones among *Enterobacteriaceae* family is increasing; therefore, it is necessary to further investigate new options for treating these infections.

Although ciprofloxacin associated with rifampin demonstrated a high success rate in a randomized trial in staphylococcal prosthetic joint infections, nowadays levofloxacin is superior to ciprofloxacin due to levofloxacin's better therapeutic index as a consequence of a lower MIC against *S. aureus* and a high serum concentration (higher bioavailability). Furthermore, its once-a-day administration facilitates the adherence to long-term treatment. The experience from our group shows that prolonged oral regimen with levofloxacin plus rifampin is well tolerated and has good results in prosthetic joint infections due to Grampositive cocci [61]. Moxifloxacin is more active than levofloxacin against staphylococci and it has moderate activity against intracellular SCV [62]; however, rifampin induces moxifloxacin metabolism reducing serum levels by approximately 30 % [63], therefore, moxifloxacin could be the best fluoroquinolone for staphylococci when rifampin cannot be administered.

The most important adverse events are gastrointestinal discomfort and diarrhea associated with *Clostridium difficile* in 1–5 % of cases. Headache, vertigo, dizziness, or convulsion (more frequent in patients with epilepsy or cranial trauma) has been described in less than 2 %. Tachycardia or other arrhythmia especially in patients with hypokalemia, hypocalcemia, and hypomagnesemia. Arthralgia and Achilles tendinitis in less than 1 % of cases.

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