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Systemic antibiotic treatment of chronic osteomyelitis in adults

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Abstract. Chronic osteomyelitis is a difficult to treat infection of the bone, which requires a combined medical and surgical approach and often persists intermittently for years, with relapses and failures. The optimal type, route of administration, and duration of antibiotic treatment remain controversial, and the emergence of multi-drug resistant organisms poses major therapeutic challenges. Identification of the causative agent and subsequent targeted antibiotic treatment has a major impact on patients' outcome. In this review, we summarize which intravenous and oral antibiotics are the best options available for the treatment of chronic osteomyelitis, according to specific aetiologies.

Key Words
Chronic osteomyelitis, Antibiotics, Targeted therapy.

Introduction

Chronic osteomyelitis is a long-lasting infection of the bone and bone marrow caused by bacteria, mycobacteria or fungi. It is not possible to identify a time threshold after which bone infection becomes chronic. It usually persists intermittently for months or years, with multiple clinical failures and relapses after periods of quiescence and apparently successful treatment, having a major impact on patients' quality of life and healthcare system costs. Chronic osteomyelitis is, therefore, a challenging medical condition for orthopaedic surgeons and infectious diseases specialists, especially from a therapeutic point of view.

At the present time, there is not a generally accepted and interdisciplinary-shared classification for chronic osteomyelitis. Several attempts of systematic classification based on pathogenesis, aetiology, host immune status and bone and soft tissues involvement have been developed in years, without reaching consensus on a unique system able to provide management and prognostic information[1].

In the majority of cases, treatment of chronic osteomyelitis requires a combined surgical and medical approach. Surgical debridement is essential to remove infected dead bone tissue, which may cause relapses months or years after the initial clinical manifestation. It is usually followed, in clinical practice, by a long course of targeted antibiotic therapy. The optimal duration of antimicrobial treatment after surgery has not been well defined. Four to six weeks of parenteral antibiotic therapy has become the standard of treatment for chronic osteomyelitis. Nevertheless, due to high failure and recurrence rates, some authors suggest longer treatments (six to eight weeks intravenously followed by three or more months of oral therapy). In cases when surgical debridement is not feasible or incomplete, even longer courses of antibiotic treatment are suggested.

The long duration and the necessity of optimal drug penetration into bone tissue are peculiar characteristics of antimicrobial treatment in chronic osteomyelitis. These two features are challenging and lead to unsolved questions regarding the selection of the best antimicrobial approach. What is the optimal route of administration at onset and in the following weeks? When and how long is parenteral therapy more effective than oral therapy? Are certain antibiotic agents preferred? What drugs allow prosecution of treatment in the outpatient setting, which is more comfortable for patients and less expensive for the healthcare system?

Microbiology

Identification of the causative pathogen should be a priority in the diagnosis of chronic osteomyelitis since it allows narrowing antibiotic spectrum and subsequently focusing on optimizing therapy in terms of pharmacokinetics, pharmacodynamics, and reduction of adverse effects.

Despite its crucial role, microbiological aetiology may be difficult to establish. Pathogen identification is based on cultures of bone samples, which are obtained through percutaneous procedures or during surgical debridement. Con-

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versely, blood cultures have high sensitivity only in acute forms of osteomyelitis and are usually not useful in the diagnosis of chronic bone infections[2]. Furthermore, superficial samples or swabs from fistulas have low accuracy when compared with bone biopsy culture and should not be used for pathogen identification[3-7].

According to current literature, a high percentage of chronic osteomyelitis cases (from 28% to 50%) are culture negative and remain microbiologically undiagnosed[7,8]. In order to increase bone culture sensitivity, some authors recommend prolonged culture (up to 14 days) for low-virulence organisms[8]. To increase sensitivity, cessation of antibiotics at least 1 to 2 weeks before cultures is strongly suggested.

Based on cultures of operative specimens, in the majority of cases (from 48% to 88% in observational studies)[7,8], chronic osteomyelitis are monomicrobial infections, while a polymicrobial aetiology is more common in post-traumatic infections[7].

Gram-positive microorganisms are the most common isolates in chronic osteomyelitis (around 60%), with a predominance of *Staphylococcus aureus* (SA)[9]. The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) among the SA isolated varies widely between studies, due to wide geographical differences and different prevalence in community and hospital settings. Gram-negative bacilli (*Pseudomonas* spp, *Enterobacteriaceae*) and anaerobes have been more frequently reported in polymicrobial aetiology cases[8,10,11]. In recent years, antimicrobial resistant organisms (mainly extended-spectrum beta-lactamases (ESBL) producing organism and multidrug resistant (MDR) Gram-negative bacteria) have been increasingly reported as causative agents of chronic osteomyelitis[8,12], posing new therapeutic challenges. A detailed description of the frequency of bacterial isolates from bone cultures reported in previous studies on chronic osteomyelitis is given in Table I.

Tubercular osteomyelitis is a well-known clinical manifestation of *Mycobacterium tuberculosis* infection, which can present in the context of disseminated disease or as an isolated localization in any bone segment.

Fungi (*Candida* spp and *Aspergillus* spp) and non-tuberculous mycobacteria may be alternative causative agents of osteomyelitis, especially in immunosuppressed patients.

Fungal and mycobacterial osteomyelitis are beyond the purpose of this paper and are not included in the present review.

Table I. Frequency of bacterial isolates from bone cultures according to what reported in previous studies on chronic osteomyelitis.

	Zuluaga AF et al[97] Arch Intern Med 2006		Sheehy SH et al[8] J Infect 2010		Jiang N et al[98] Medicine (Baltimore) 2015		Vemu L et al[7] J Lab Physicians. 2018	
	N°	%	N°	%	N°	%	N°	%
Sterile cultures	6	4	47	28.3	89	29.4	42	37.2
Staphylococcus aureus	43	28.7	52	31.3	59	34.9	45	39.8
– MSSA	NR		36		NR		15	
– MRSA	NR		16		NR		30	
CoNS	13	8.7	27	16.3	NR	---	NR	---
Streptococcus spp.	10	6.7	12	7.2	NR	---	2*	1.8
Enterococcus spp.	22	14.7	8		10	3.3	NR	
– *E. faecalis*	19		NR	4.8	10			
– *E. faecium*	2		NR		NR			
– Other spp.	1		NR		NR			
EGNB	24	16	27	16.3	30	9.9	24	21.2
Pseudomonas spp.	15	10	9	5.4	29§	17.2	4§	3.5
Anaerobes	16	10.7	15	9	NR	---	NR	---
Others	1	0.7	14	8.4	6	2	1	0.9
Total	150		166		303		113	

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, coagulase-negative staphylococci; EGNB, enteric gram-negative bacteria; NR, not reported.
*only *Streptococcus*. pyogenes reported; §only *Pseudomonas aeruginosa* reported

Treatment: general and surgical management

Management of chronic osteomyelitis requires a combined surgical and medical approach, involving an aggressive surgical debridement followed by a long course of antibiotic therapy[13]. Adequate surgical debridement with removal of all dead and ischemic tissues and sinus tracts is the cornerstone of successful treatment. The only curative strategy is a wide surgical excision including healthy bone and soft tissues, as in an oncological approach[14], since local and conservative debridement is associated with high failure rates[2,15]. This aggressive approach has two clinical benefits: it allows complete removal of the infected bone and biofilm and guarantees an adequate vascular supply, favouring subsequent antibiotic activity. Therefore, surgical debridement should be considered preliminary to antibiotic therapy. The role of surgery is not limited to surgical debridement but involves three adjunctive aspects that contribute to treatment success: adequate management of dead space (which is the bone defect present after debridement, usually filled with muscle flaps, bone graft, calcium hydroxyapatite implants or temporarily with polymethylmethacrylate beads with or without antibiotic), stabilization of the bone[16] and wound site coverage by skin grafts[2,10,17-23].

Treatment: systemic antibiotic therapy

Clinical randomized trials addressing the best appropriate agent, route of administration and duration of therapy in chronic osteomyelitis are lacking. Therefore, current practice and recommendations are based on retrospective observational studies, expert opinion and data from animal and in vitro experimental studies.

General Principles and Route of Administration

Penetration of antibiotics into bone tissue has been extensively studied, but data show substantial variability between drugs and between different studies of the same drug. In general, bone penetration is low, achieving a bone to serum concentration ratio of maximum 0.3 for the majority of antibiotics[24].

To overcome the problem of diffusion into infected bone, antibiotics in the treatment of osteomyelitis have been classically administered intravenously, in order to achieve the highest possible plasma concentrations and subsequent tissue penetration. This applies particularly to drugs that have poor bioavailability (β-lactams) or are not absorbed at all when taken orally, such as glycopeptides and lipopeptide agents (i.e., vancomycin, teicoplanin, daptomycin, oritavancin, dalbavancin, and telavancin), colistin, aminoglycosides, and tigecycline.

Parenteral administration may be theoretically intravenous or intramuscular. Nevertheless, intramuscular route is often difficult because of the prolonged duration of treatment and the concomitant anticoagulation therapy patients may receive in the post-surgical period, reducing the choice for parenteral therapy to the intravenous route. The need of prolonged intravenous therapy often requires the implantation of a central venous catheter, which exposes the patient to catheter-related complications such as infective and thrombotic events, with subsequent notably higher management costs[25].

Consequently, increasing attention has been drawn to antibiotics with high oral bioavailability and various studies have tried to compare the efficacy of oral and intravenous administration. Interestingly, the antibiotics that achieve the highest bone to serum concentration ratios (fluoroquinolones, sulfamides, cyclines, macrolides, rifamycins, and oxazolidinones) are also those with the highest oral bioavailability, making these agents good candidates for the prolonged treatment of outpatients with chronic osteomyelitis. In a recent review by Conterno et al[26] in 2013, which confirmed the results of Spellberg[27] et al in 2012, no statistically significant difference was found between oral versus parenteral antibiotics for the treatment of osteomyelitis if the bacteria were sensitive to the antibiotic used. This finding outlines the importance of a pathogen-specific therapy and encourages further studies to compare differences in clinical efficacy and adverse events between oral versus parenteral administration of systemic antibiotics for treating chronic osteomyelitis in adults.

Combination therapy is suggested in selected cases in order to reduce the possibility of selecting resistant organisms and/or to add agents with expected activity on biofilm.

Pathogen-Specific Treatment

Delaying the start of antibiotic treatment until bone culture and identification of the causative organism is a cornerstone in treating chronic osteomyelitis. In almost all cases, the antibiotic therapy of chronic osteomyelitis is not an emergency, and the indolent and sub-acute nature of the infection usually allows to waiting for culture results and starting a tailored therapy. Below, a review of old and new an-

tibiotics commonly used and/or potentially active in treating chronic osteomyelitis, divided by causative agent. A summary of organism-specific preferred antibiotic agents is given in Table II.

Gram-positive organisms: Staphylococci

Methicillin-susceptible Staphylococcus aureus (MSSA) and coagulase-negative staphylococci (CoNS)

Anti-staphylococcal parenteral b-lactam agents, i.e., oxacillin, nafcillin, and cefazolin, are suitable options for initial treatment of chronic staphylococcal osteomyelitis[2]. Unfortunately, these agents are not available in oral formulation and bioavailability of oral penicillin and cephalosporins is usually low. Therefore, switching to oral therapy often requires a change towards other agents usually active against both MSSA and MRSA, such as doxycycline, clindamycin or trimethoprim-sulfamethoxazole (TMP-SMX). In patients with penicillin allergy, clindamycin and vancomycin are good therapeutic alternatives.

Methicillin-resistant Staphylococcus aureus (MRSA) and coagulase-negative staphylococci (CoNS)

Glycopeptides, such as vancomycin and teicoplanin, have been considered the main agents of choice against MRSA in treating osteomyelitis. Both of them are only available in parenteral formulation. Vancomycin has long been utilized as the first-choice agent due to its long history of use, available clinical data and relatively easy-to-use pharmacokinetic dosing nomograms[28]. Nevertheless, it has an elevated risk of adverse events, in particular of acute renal failure, especially in patients with other risk factors such as concomitant use of nephrotoxic agents, high trough serum concentrations or prolonged administration[29]. Moreover, even in the case of a MRSA strain considered susceptible to vancomycin, the population may contain vancomycin-resistant (VRSA) or vancomycin-intermediate (VISA) subpopulations (heteroresistant strains), which may potentially make the drug less effective. Teicoplanin is associated with a lower rate of adverse events compared to vancomycin[30,31], and it has generally lower minimum inhibitory concentrations (MICs) than vancomycin for SA, whereas CoNS MICs are usually lower for vancomycin.

Rifampicin is an old antibiotic with two main characteristics that make it an agent of choice in the treatment of staphylococcal chronic osteomyelitis: it exhibits a bactericidal activity against staphylococci in the sessile phase, as found in biofilm, and has high intracellular activity, which is useful in chronic osteomyelitis since bacteria can persist inside phagocytes[32,33]. Notably, rifampicin should never be used as monotherapy for staphylococcal osteomyelitis because of it often selects rifampicin-resistant mutants, particularly if started with high levels of bacterial inoculum, i.e., at the beginning of treatment[34]. Combination of rifampicin with another active antibiotic for the treatment of chronic osteomyelitis has been shown to have better outcomes when compared to regimen without rifampicin[35,36]. Therefore, rifampicin is considered the backbone agent in killing staphylococci in biofilm and chronic osteomyelitis and its combination with other antibiotics, especially levofloxacin, is mandatory to prevent the selection of resistance[37-39].

The emergence of vancomycin intermediate and resistant SA strains, along with low tolerability profile and suboptimal cure rates, has recently led to the development and approval by the FDA and EMA of several new antibiotics with activity against resistant Gram-positive bacteria.

Daptomycin is a lipophilic lipopeptide, with a bactericidal effect and a spectrum of activity similar to vancomycin, even though it shows lower MICs against MSSA and MRSA and it is usually active against vancomycin-resistant SA strains. Moreover, daptomycin has a concentration-dependent bactericidal activity and in vitro studies have demonstrated higher cure rates when administered at an increased dose (10 mg/kg/day instead of the standard dose of 6 mg/kg/day) and in combination with rifampicin[40,41]. It is currently approved by FDA and EMA for treatment of complicated skin and skin structure infections (cSSSIs) and SA bloodstream infections (BSI), including those due to right-sided endocarditis. Nonetheless, in vitro studies have demonstrated that the diffusion of daptomycin into bone tissues is close to that of beta-lactams and glycopeptides, which is enough to maintain bone concentrations several times higher than MICs of most Gram-positive cocci[42]. Moreover, most published clinical data describing its use in treating acute osteomyelitis, mainly derived from the CORE and Eu-CORE database, show non-inferiority of daptomycin when compared with vancomycin[43-46]. Daptomycin can only be administered parenterally and is usually well tolerated: it is safe in patients at any stage of renal dysfunction and its main adverse effect is the elevation of creatine phosphokinase (CPK) and, in rare cases, rhabdomyolysis. Taking into account available clinical data, along with its pharmacokinetics/pharmacodynamics and safety profile, in selected cases, daptomycin may be considered a valid agent in the treatment of Gram-positive chronic osteomyelitis.

Table II. Agents commonly used in targeted antibiotic treatment of chronic osteomyelitis (new drugs with small experience in the treatment of chronic osteomyelitis but potentially active according to spectrum and PK/PD characteristics are in italics).

	IV treatment	PO treatment
MSSA and MS-CoNS	Preferred regimens: • Nafcillin 2 g q4h • Oxacillin 2 g q4h • Cefazolin 2 g q8h Alternative regimens: • Clindamycin 600 mg q6h or 900 mg q8h • Vancomycin 15 mg/kg q12h (dose should be adjusted to maintain a trough level of 15-20 µg/mL) • Teicoplanin 6-12 mg/kg q12h x3 doses, then 6-12 mg/kg q24h • Daptomycin 6 mg/kg q24h • Linezolid 600 mg q12h	• Doxycycline 100 mg q12h • Clindamycin 450 mg q6h • TMP-SMX DS tablet (160/800 mg) 1-2 tablets q8-12h • Rifampicin 600 mg PO daily or 300-450 mg q12hr* • Levofloxacin 750 mg q24h or moxifloxacin 400 mg q24h
MRSA and MR-CoNS	Preferred regimens: • Vancomycin 15 mg/kg q12h (dose should be adjusted to maintain a trough level of 15-20 µg/mL) • Teicoplanin 6-12 mg/kg q12h x3 doses, then 6-12 mg/kg q24h • Daptomycin 6 mg/kg q24h • Linezolid 600 mg q12h Alternative regimens: • Clindamycin 600 mg q6h or 900 mg q8h • *Dalbavancin 1000 mg once, followed by 500 mg weekly* • *Tedizolid 200 mg q24h* • *Fosfomycin 12-24 g/daily, divided into* 3 doses	• Doxycycline 100 mg q12h • Clindamycin 450 mg q6h • TMP-SMX DS tablet (160/800 mg) 1-2 tablets q8-12h • Rifampicin 600 mg PO daily or 300-450 mg q12hr* • Levofloxacin 750 mg q24h or moxifloxacin 400 mg q24h • Linezolid 600 mg q12h • *Tedizolid 200 mg q24h*
Streptococcus spp.	Preferred regimens: • Penicillin G 6 MU q6h • Ceftriaxone 2 g q24h • Ampicillin 2 g q4h or 3g q6h Alternative regimens: • Clindamycin 600 mg q6h or 900 mg q8h • Vancomycin 15 mg/kg q12h (dose should be adjusted to maintain a trough level of 15-20 µg/mL) • Teicoplanin 6-12 mg/kg q12h x3 doses, then 6-12 mg/kg q24h • Daptomycin 6 mg/kg q24h • Linezolid 600 mg q12h • Dalbavancin 1000 mg once, followed by 500 mg weekly	• Amoxicillin 500 mg q8h • Clindamycin 450 mg q6h • Levofloxacin 750 mg q24h or moxifloxacin 400 mg q24h
Enterococcus spp.	• Ampicillin 2 g q4h or 3g q6h§ • Vancomycin 15 mg/kg q12h (dose should be adjusted to maintain a trough level of 15-20 µg/mL) • Teicoplanin 6-12 mg/kg q12h x3 doses, then 6-12 mg/kg q24h • Daptomycin 6 mg/kg q24h • Linezolid 600 mg q12h • *Tedizolid 200 mg q24h* • *Tigecycline 100 mg loading dose, followed by 50 mg q12h*	• Amoxicillin/clavulanate 1 g q8h • Levofloxacin 750 mg q24h or moxifloxacin 400 mg q24h • Ceftriaxone 2 g q24h
EGNB (other than *Pseudomonas*)	• Ciprofloxacin 400 mg q12h • Piperacillin/tazobactam 4.5 g q8h • Meropenem 1 g q8h or ertapenem 1 g q24h	• Ciprofloxacin 500-750 mg q12h

Continued

Table II (Continued). Agents commonly used in targeted antibiotic treatment of chronic osteomyelitis (new drugs with small experience in the treatment of chronic osteomyelitis but potentially active according to spectrum and PK/PD characteristics are in italics).

	IV treatment	PO treatment
Pseudomonas spp.	• Ceftazidime 2 g q8h • Cefepime 2g q8h • Piperacillin/tazobactam 4.5 g q6h • Ciprofloxacin 400 mg q8h • Meropenem 1 g q8h	• Ciprofloxacin 750 mg q12h
MDR-GNB	• Fosfomycin 12-24 g/daily, divided into 3 doses • *Gentamicin 5-7 mg/kg q24h or amikacin 15 mg/kg q24h* • *Colistin 9 MU loading dose, fllowed by 4.5 MU q12h* • *Tigecycline 100 mg loading dose, followed by 50 mg q12h* • *Ceftolozane/tazobactam 1.5 g q8h* • *Ceftazidime/avibactam 2.5 g q8h* • *Meropenem/varbobactam 4 g q8h*	
Anaerobes	• Amoxicillin/clavulanate 2.2 g q8h or q6h • Piperacillin/tazobactam 4.5 g q8h • Clindamycin 600 mg q6h or 900 mg q8h • Metronidazole 500 mg q8h • Amoxicillin/clavulanate 1 g q8h • Clindamycin 450 mg q6h • Metronidazole 500 mg q8h	

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus;* MRSA, methicillin-resistant *Staphylococcus aureus;* MS-CoNS, methicillin-susceptible coagulase-negative Staphylococci; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; TMP-SMX, trimethoprim-sulfamethoxazole; DS, double-strenght; MU, million units; EGNB, enteric gram-negative bacteria; MDR-GNB, multidrug-resistant gram-negative bacteria.
*It should never be used as monotherapy; §*E. faecium* is intrinsically resistant to all beta-lactams; Systemic antibiotic treatment of chronic osteomyelitis

New lipoglycopeptides (telavancin, oritavancin, dalbavancin) with potent activity against Gram-positive organisms (most notably staphylococci including MRSA and to some extent VISA, streptococci, and clostridia) have recently been developed[47]. The main characteristic of these molecules is the remarkably long half-life of oritavancin and dalbavancin, which allow for infrequent dosing (single dose of 1200 mg for oritavancin and 1000 mg at day 1 followed by 500 mg at day 8 for dalbavancin) and may be exploited for the prosecution of outpatient therapy. Moreover, these molecules showed to be highly active in *in vitro* biofilm models, proving an equal or even major efficacy in eradicating infection when compared to vancomycin[48-50]. In 2015, Dunne et al[51] studied the distribution of dalbavancin into bone and articular tissues, demonstrating to reach high concentrations in cortical bone and warranting investigation in the use of this drug for the treatment of osteomyelitis. More recently, Pfaller et al[52] demonstrated MICs for dalbavancin at least eight-fold lower than comparators (vancomycin, linezolid, daptomycin, and clindamycin) against SA isolated from patients with bone and joint infections. Lipoglycopeptides are currently approved only for the treatment of acute bacterial skin and skin structure infections (SSTIs), with the exception of telavancin even for hospital-acquired (HAP) and ventilator-associated bacterial pneumonia (VAP). Nevertheless, the usefulness of these drugs in other potential indications has been examined in case reports and small series of patients. Telavancin has been successfully used in the treatment of acute and chronic osteomyelitis in four cases[53,54], while dalbavancin showed a success rate of 91% in 12 patients treated for osteomyelitis in a recent clinical retrospective study by Bouza et al[55].

Linezolid is a synthetic oxazolidinone antibiotic, with activity against all Gram-positive cocci including MRSA[56], vancomycin-resistant enterococci (VRE) and obligate anaerobes. It has high bioavailability and is available in oral formulation, which makes it an attractive option in the treatment of chronic osteomyelitis. It is approved for SSTIs, including diabetic foot infection, and pneumonia.

Pharmacokinetic studies aimed to evaluate linezolid penetration into bone tissue found mixed results with a variable bone to plasma ratios in different experimental model[42, 57-59], even though many case series reported its use in the treatment of osteomyelitis and joint infections, usually as salvage therapy for patients who have failed previous antibiotic regimens. Overall, linezolid has demonstrated high success rates in these reports, with a combined cure rate of 83% (286/343)[4, 60-68]. The main limitation in the use of linezolid relies in its numerous side effects including thrombocytopenia, anaemia, optic neuritis, and peripheral neuropathy[4,69-71]. In particular, bone marrow suppression and anaemia seem to increase with long-term therapy and may limit linezolid's potential use in chronic osteomyelitis treatment. Anecdotally, it has been recently shown that the association of linezolid with rifampicin may result in a decreasing occurrence of anaemia in cases of prolonged treatment, probably as a consequence of the induction of extrarenal clearance of linezolid by rifampicin[61,72].

Tedizolid is a second-generation oxazolidinone that displays a potent activity against Gram-positive pathogens. It is approved only for the treatment of acute SSTIs and is available in oral formulation. There is scarce evidence on its use in the treatment of bone infections. A recent study by Ract et al[73] of 359 clinical isolates involved in clinically documented bone and joint infections showed a potent *in vitro* activity of tedizolid against most Gram-positive pathogens, including MRSA and CoNS strains. Current evidence is not sufficient to support its use in the treatment of osteomyelitis, lacking data on its bone penetration and safety profile on long-term therapy, even though in Phase 3 clinical studies tedizolid showed mainly gastrointestinal adverse effects, apparently without adverse effects on the bone marrow.

Fluoroquinolones are active against Staphylococci *in vitro* and have shown their activity in animal models of chronic implant-associated staphylococcal infections[74,75]. Their main advantage is a high bioavailability, which makes them optimal agents for long-term oral therapy in chronic osteomyelitis. Moreover, all fluoroquinolones have high bone penetration and therefore can be used in the treatment of osteomyelitis. Among them, newer fluoroquinolones (such as levofloxacin, moxifloxacin, gatifloxacin, and gemifloxacin) tend to have lower MICs for Gram-positive pathogens than older fluoroquinolones (such as ciprofloxacin and ofloxacin)[76] do and have a higher barrier to the emergence of resistance[77]. Therefore, some authors suggest the use of fluoroquinolones in monotherapy in the treatment of osteomyelitis[78], while others advocate their use *in vivo* in combination with other agents, due to the possibility to induce resistance during monotherapy[79]. In conclusion, newer fluoroquinolones are preferred over older fluoroquinolones as anti-staphylococcal agents in the treatment of chronic osteomyelitis, if possible in combination therapy, but monotherapy may be employed when alternative regimens are not available. Older fluoroquinolones should never be used in monotherapy in the treatment of staphylococcal infections.

Tigecycline is a glycylcycline with a very broad-spectrum of activity: it covers most of the Gram-positive pathogens, including MRSA and VRE, some Gram-negatives and anaerobes. It is currently approved for the treatment of cSSSIs and of complicated intra-abdominal infections. Its main side effects are nausea, vomiting, and diarrhoea. Data regarding bone penetration and clinical outcomes of tigecycline in the treatment of osteomyelitis are lacking, not sufficient to support its use in cases sustained by Gram-positive agents[80-83]. In addition, recent meta-analyses showed excess deaths when using tigecycline both in approved and non-approved indications, suggesting that it should not be used in serious infections[84,85].

Satisfactory results have been reported in terms of clinical outcomes and tolerability profile in the treatment of chronic osteomyelitis with other agents, such as TMP-SMX, clindamycin and intravenous fosfomycin[86].

Streptococcus spp and Enterococcus spp

Streptococci are rarely the causative agent of chronic osteomyelitis, being instead mostly isolated in acute cases, especially in paediatric patients. Streptococcal osteomyelitis is often related to beta-haemolytic streptococci, and its parenteral treatment is based on penicillin G and A (ampicillin or amoxicillin) and parenteral first-, second- or third-generation cephalosporins. Oral formulations available are limited to Penicillin A (mainly amoxicillin due to the unfavourable PK/PD profile of ampicillin) and to first and second-generation cephalosporins due to the weak bioavailability of oral third-generation cephalosporins. Moreover, oral beta-lactams generally have poor activity and are not valid options in cases of chronic osteomyelitis. Clindamycin, linezolid, glycopeptides, daptomycin, and the new lipoglycopeptides are active against Streptococci and may be valid options in cases of beta-lactams allergy.

Enterococcal chronic osteomyelitis are mainly due to *Enterococcus faecalis* and *Enterococcus faecium*. *E. faecalis* is usually susceptible to penicillin G and A, while *E. faecium* is intrinsically resistant to all beta-lactams and may be resistant to glycopeptides, mainly due to the expression of VanA and VanB phenotypes. In these situations, therapeutic options are restricted to linezolid (which has the advantage of being available in oral formulation), daptomycin and tigecycline, despite lack of evidence on its efficacy in bone and joint infections. Notably, among the new lipoglycopeptides, only oritavancin has shown to be active against VRE, while dalbavancin and telavancin are not active against VanA phenotypes and should not be used in the treatment of VRE infections[87].

Gram-negative organisms

Gram-negative bacteria are an increasing cause of chronic osteomyelitis, even though very few studies evaluating their follow-up and outcomes are available in the literature[88]. Classical parenteral options include penicillin-beta-lactamase inhibitor combination drugs, cephalosporins, aztreonam, carbapenems, and aminoglycosides. In particular, in a prospective randomized open-label trial, Barberàn et al[89] reported a cure rate of 71% in patients with osteomyelitis treated with cefepime. Among carbapenems, ertapenem has a long half-life, which allows single daily intravenous administration, making it an attractive option for outpatient therapy.

The number of oral agents available for the treatment of the Gram-negative osteomyelitis is more limited than for Gram-positive osteomyelitis. Fluoroquinolones appear to be the first-line choice in this setting, due to their anti-biofilm activity and to the results of experimental studies that established their superiority over other agents for the treatment of Gram-negative osteomyelitis, both alone and in combination with other agents[90,91]. TMP-SMX and tetracyclines, such as doxycycline and minocycline, are considered alternative options.

Pseudomonas spp

The treatment of osteomyelitis due to *Pseudomonas* spp. is based on a limited number of antibiotic agents, such as piperacillin-tazobactam, ceftazidime, cefepime, ciprofloxacin, aztreonam, carbapenems (except for ertapenem that is not active against *Pseudomonas* spp), aminoglycosides, and colistin. It is therefore considered a difficult-to-treat organism, and it has been demonstrated that *Pseudomonas* spp. osteomyelitis failure rates are three times higher than that of staphylococcal osteomyelitis[92].

MDR Gram-negative bacteria

With the rise in prevalence and diffusion of MDR Gram-negative bacteria, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and carbapenem-resistant *Enterobacteriaceae* (CRE), cases of chronic osteomyelitis caused by these agents have been described in literature, especially in diabetic foot infections[12], and they are likely to increase in number in future years. In these cases, very few therapeutic options are available and are restricted to aminoglycosides, colistin, tigecycline, and intravenous fosfomycin, despite their unknown bone penetration profile and the scarce or null evidence of efficacy of these agents in treating osteomyelitis. In particular, Tascini et al[93] described the use of colistin in treating 4 cases of diabetic foot infection complicated by osteomyelitis, stating its safety and effectiveness when used alone or in combination with other antimicrobial agents.

The use of new betalactams-betalactamases inhibitors, such as ceftolozane/tazobactam, ceftazidime/avibactam, and meropenem/varbobactam, have never been reported in the treatment of osteomyelitis and their bone penetration profile is unknown. Therefore, they should be taken into consideration only in selected cases and when other therapeutic options are not available.

Obligate anaerobes

Metronidazole is the drug of choice for treatment of chronic osteomyelitis caused by obligate anaerobic bacteria (except for *Propionibacterium acnes*), due to its high oral bioavailability, remarkable killing ability, and excellent tissue diffusion. Other antibiotics that are active against strict anaerobes and may be considered as alternative agents are amoxicillin-clavulanate, piperacillin-tazobactam, carbapenems, and clindamycin (resistance of *Bacteroides* spp. is around 20%). Linezolid and tigecycline are active against obligate anaerobes but they are considered second-line agents and should be reserved to selected cases.

Duration

It is common opinion and practice that chronic osteomyelitis requires a prolonged antibiotic therapy. However, the optimal duration of treatment is not known. Most experts favour continuing antibiotics intravenously at least for 4-6 weeks

after surgical debridement, which is considered the time the debrided bone takes to be covered by vascularized soft tissue. A following long-term antibiotic therapy with an oral agent (3 to 6 months) is usually warranted due to the low penetration of antimicrobials into bone tissue and to the high rate of recurrence[94-97].

In case of suboptimal surgical debridement, or in patients unwilling or unable to undergo surgical intervention, is common practice to continue a prolonged suppressive antibiotic therapy, similarly to the approach in the treatment of prosthetic joint infection when removal of the prosthesis is not feasible[97-99].

Conclusions

Despite the expanding therapeutic armamentarium, chronic osteomyelitis remains a challenging and difficult-to-treat clinical situation, with frequent recurrences, the latency of infection and significant impact on patients' quality of life. Clearly, more research is warranted to determine for each causative agent of osteomyelitis the most appropriate antibiotic, duration, dose, and route of administration in the perspective of antimicrobial stewardship.

Conflicts of interest statement

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1) Hotchen AJ, McNally MA, Sendi P. The classification of long bone osteomyelitis: a systemic review of the literature. J Bone Jt Infect 2017; 2: 167-174.
2) Lew DP, Waldvogel FA. Osteomyelitis. Lancet 2004; 364: 369-379.
3) Perry CR, Pearson RL, Miller GA. Accuracy of cultures of material from swabbing of the superficial aspect of the wound and needle biopsy in the preoperative assessment of osteomyelitis. J Bone Joint Surg Am 1991; 73: 745-749.
4) Senneville E, Melliez H, Beltrand E, Legout L, Valette M, Cazaubiel M, Cordonnier M, Caillaux M, Yazdanpanah Y, Mouton Y. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. Clin Infect Dis 2006; 42: 57-62.
5) Senneville E, Morant H, Descamps D, Dekeyser S, Beltrand E, Singer B, Caillaux M, Boulogne A, Legout L, Lemaire X, Lemaire C, Yazdanpanah Y. Needle puncture and transcutaneous bone biopsy cultures are inconsistent in patients with diabetes and suspected osteomyelitis of the foot. Clin Infect Dis 2009; 48: 888-893.
6) Zuluaga AF, Galvis W, Jaimes F, Vesga O. Lack of microbiological concordance between bone and non-bone specimens in chronic osteomyelitis: an observational study. BMC Infect Dis 2002; 2: 8.
7) Vemu L, Sudhaharan S, Mamidi N, Chavali P. Need for appropriate specimen for microbiology diagnosis of chronic osteomyelitis. J Lab Physicians 2018; 10: 21-25.
8) Sheehy SH, Atkins BA, Bejon P, Byren I, Wyllie D, Athanasou NA, Berendt AR, McNally MA. The microbiology of chronic osteomyelitis: prevalence of resistance to common empirical anti-microbial regimens. J Infect 2010; 60: 338-343.
9) Kavanagh N, Ryan EJ, Widaa A, Sexton G, Fennell J, O'Rourke S, Cahill KC, Kearney CJ, O'Brien FJ, Kerrigan SW. Staphylococcal osteomyelitis: disease progression, treatment challenges, and future directions. Clin Microbiol Rev 2018; 31.
10) Waldvogel FA, Papageorgiou PS. Osteomyelitis: the past decade. N Engl J Med 1980; 303: 360-370.
11) Carek PJ, Dickerson LM, Sack JL. Diagnosis and management of osteomyelitis. Am Fam Physician 2001; 63: 2413-2420.
12) Saltoglu N, Ergonul O, Tulek N, Yemisen M, Kadanali A, Karagoz G, Batirel A, Ak O, Sonmezer C, Eraksoy H, Cagatay A, Surme S, Nemli SA, Demirdal T, Coskun O, Ozturk D, Ceran N, Pehlivanoglu F, Sengoz G, Aslan T, Akkoyunlu Y, Oncul O, Ay H, Mulazimoglu L, Erturk B, Yilmaz F, Yoruk G Uzun N, Simsek F, Yildirmak T, Yaşar KK, Sonmezoglu M, Küçükardali Y, Tuna N, Karabay O, Ozgunes N, Sargin F; Turkish Society of Clinical Microbiology and Infectious Diseases, Diabetic Foot Infections Study Group. Influence of multidrug resistant organisms on the outcome of diabetic foot infection. Int J Infect Dis 2018; 70: 10-14.
13) Senneville E, Nguyen S. Current pharmacotherapy options for osteomyelitis: convergences, divergences and lessons to be drawn. Expert Opin Pharmacother 2013; 14: 723-734.
14) Forsberg JA, Potter BK, Cierny G, Webb L. Diagnosis and management of chronic infection. J Am Acad Orthop Surg 2011; 19 Suppl 1: S8-S19.
15) Simpson AH, Deakin M, Lathan JM. The effect of the extent of surgical resection on infectionfree survival. J Bone Joint Surg Br 2001; 83: 403-407.
16) Hahn BS, Kim KH, Kuh SU, Park JY, Chin DK, Kim KS, Cho YE. Surgical treatment in patients with cervical osteomyelitis: single institute's experiences. Korean J Spine 2014; 11: 162-168.
17) Ciampolini J, Harding KG. Pathophysiology of chronic bacterial osteomyelitis. Why do antibiotics fail so often? Postgrad Med J 2000; 76: 479-483.
18) Eckardt JJ, Wirganowicz PZ, Mar T. An aggressive surgical approach to the management of chronic osteomyelitis. Clin Orthop Relat Res 1994; 298: 229-239.

19) Haidar R, Der Boghossian A, Atiyeh B. Duration of post-surgical antibiotics in chronic osteomyelitis: empiric or evidence-based? Int J Infect Dis 2010; 14: e752-758.
20) Mader JT, Mohan D, Calhoun J. A practical guide to the diagnosis and management of bone and joint infections. Drugs 1997; 54: 253-264.
21) Mader JT, Shirtliff ME, Bergquist SC, Calhoun J. Antimicrobial treatment of chronic osteomyelitis. Clin Orthop Relat Res 1999; (360): 47-65.
22) Parsons B, Strauss E. Surgical management of chronic osteomyelitis. Am J Surg 2004; 188: 57-66.
23) Walter G, Kemmerer M, Kappler C, Hoffmann R. Treatment algorithms for chronic osteomyelitis. Dtsch Arztebl Int 2012; 109: 257-264.
24) Landersdorfer CB, Bulitta JB, Kinzig M, Holzgrabe U, Sörgel F. Penetration of antibacterials into bone: pharmacokinetic, pharmacodynamic and bioanalytical considerations. Clin Pharmacokinet 2009; 48: 89-124.
25) Pulcini C, Couadau T, Bernard E, Lorthat-Jacob A, Bauer T, Cua E, Mondain V, Chichmanian RM, Dellamonica P, Roger PM. Adverse effects of parenteral antimicrobial therapy for chronic bone infections. Eur J Clin Microbiol Infect Dis 2008; 27: 1227-1232.
26) Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev 2013; (9): CD004439.
27) Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis 2012; 54: 393-407.
28) Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC Jr, Craig WA, Billeter M, Dalovisio JR, Levine DP. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2009; 29: 1275-1279.
29) Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 2009; 49: 507-514.
30) Svetitsky S, Leibovici L, Paul M. Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. Antimicrob Agents Chemother 2009; 53: 4069-4079.
31) LeFrock J, Ristuccia A. Teicoplanin in the treatment of bone and joint infections: an open study. J Infect Chemother 1999; 5: 32-39.
32) Saginur R, Stdenis M, Ferris W, Aaron SD, Chan F, Lee C, Ramotar K. Multiple combination bactericidal testing of staphylococcal biofilms from implant-associated infections. Antimicrob Agents Chemother 2006; 50: 55-61.
33) Yamaoka T. The bactericidal effects of anti-MRSA agents with rifampicin and sulfamethoxazole-trimethoprim against intracellular phagocytized MRSA. J Infect Chemother 2007; 13: 141-146.
34) Wehrli W. Rifampin: mechanisms of action and resistance. Rev Infect Dis 1983; 5 Suppl 3: S407-411.
35) Van der Auwera P, Klastersky J, Thys JP, Meunier-Carpentier F, Legrand JC. Double-blind, placebo-controlled study of oxacillin combined with rifampin in the treatment of staphylococcal infections. Antimicrob Agents Chemother 1985; 28: 467-472.
36) Norden CW, Bryant R, Palmer D, Montgomerie JZ, Wheat J. Chronic osteomyelitis caused by Staphylococcus aureus: controlled clinical trial of nafcillin therapy and nafcillin-rifampin therapy. South Med J 1986; 79: 947-951.
37) Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA 1998; 279: 1537-1541.
38) Senneville E, Joulie D, Legout L, Valette M, Dezèque H, Beltrand E, Roselé B, d'Escrivan T, Loïez C, Caillaux M, Yazdanpanah Y, Maynou C, Migaud H. Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to Staphylococcus aureus. Clin Infect Dis 2011; 53: 334-340.
39) Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, Sánchez-Somolinos M, Baraia-Etxaburu JM, Rico A, Palomino J, Rodríguez-Pardo D, Horcajada JP, Benito N, Bahamonde A, Granados A, del Toro MD, Cobo J, Riera M, Ramos A, Jover-Sáenz A, Ariza J; REIPI Group for the Study of Prosthetic Infection. A large multicenter study of methicillin-susceptible and methicillin-resistant Staphylococcus aureus prosthetic joint infections managed with implant retention. Clin Infect Dis 2013; 56: 182-194.
40) Garrigós C, Murillo O, Euba G, Verdaguer R, Tubau F, Cabellos C, Cabo J, Ariza J. Efficacy of usual and high doses of daptomycin in combination with rifampin versus alternative therapies in experimental foreign-body infection by methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 2010; 54: 5251-5256.
41) Parra-Ruiz J, Bravo-Molina A, Pena-Monje A, Hernandez-Quero J. Activity of linezolid and high-dose daptomycin, alone or in combination, in an in vitro model of Staphylococcus aureus biofilm. J Antimicrob Chemother 2012; 67: 2682-2685.
42) Traunmüller F, Schintler MV, Metzler J, Spendel S, Mauric O, Popovic M, Konz KH, Scharnagl E, Joukhadar C. Soft tissue and bone penetration abilities of daptomycin in diabetic patients with bacterial foot infections. J Antimicrob Chemother 2010; 65: 1252-1257
43) Rolston KV, Segreti J, Lamp KC, Friedrich LV. Cubist outcomes registry and experience (CORE) methodology. Am J Med 2007; 120: 54-55.
44) Lamp KC, Fridrich LV, Mendez-Vigo L, Russo R. Clinical experience with daptomycin for the treatment of patients with osteomyelitis. Am J Med 2007; 120: S13-S20.
45) Gonzalez-Ruiz A, Beiras-Fernandez A, Lehmkuhl H, Seaton RA, Loeffler J, Chaves RL. Clinical experience with daptomycin in Europe: the first 2.5 years. J Antimicrob Chemother 2011; 66: 912-919.

46) Seaton RA, Malizos KN, Viale P, Gargalianos-Kakolyris P, Santantonio T, Petrelli E, Pathan R, Heep M, Chaves RL. Daptomycin use in patients with osteomyelitis: a preliminary report from the EU-CORE(SM) database. J Antimicrob Chemother 2013; 68: 1642-1649.
47) Moenster RP, Linneman TW, Call WB, Kay CL, McEvoy TA, Sanders JL. The potential role of newer gram-positive antibiotics in the setting of osteomyelitis of adults. J Clin Pharm Ther 2013; 38: 89-96.
48) Barcia-Macay M, Lemaire S, Mingeot-Leclercq MP, Tulkens PM, Van Bambeke F. Evaluation of the extracellular and intracellular activities (human THP-1 macrophages) of telavancin versus vancomycin against methicillin-susceptible, methicillin-resistant, vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus. J Antimicrob Chemother 2006; 58: 1177-1184.
49) Garcia LG, Lemaire S, Kahl BC, Becker K, Proctor RA, Denis O, Tulkens PM, Van Bambeke F. Pharmacodynamic evaluation of the activity of antibiotics against hemin- and menadione-dependent small-colony variants of Staphylococcus aureus in models of extracellular (broth) and intracellular (THP-1 monocytes) infections. Antimicrob Agents Chemother 2012; 56: 3700-3711.
50) Nguyen HA, Denis O, Vergison A, Theunis A, Tulkens PM, Struelens MJ, Van Bambeke F. Intracellular activity of antibiotics in a model of human THP-1 macrophages infected by a Staphylococcus aureus small-colony variant strain isolated from a cystic fibrosis patient: pharmacodynamic evaluation and comparison with isogenic normal-phenotype and revertant strains. Antimicrob Agents Chemother 2009; 53: 1434-1442.
51) Dunne MW, Puttagunta S, Sprenger CR, Rubino C, Van Wart S, Baldassarre J. Extended-duration dosing and distribution of dalbavancin into bone and articular tissue. Antimicrob Agents Chemother 2015; 59: 1849-1855.
52) Pfaller MA, Flamm RK, Castanheira M, Sader HS, Mendes RE. Dalbavancin in-vitro activity obtained against gram-positive clinical isolates causing bone and joint infections in US and European hospitals (2011-2016). Int J Antimicrob Agents 2018; 51: 608-611.
53) Twilla JD, Gelfand MS, Cleveland KO, Usery JB. Telavancin for the treatment of methicillin-resistant Staphylococcus aureus osteomyelitis. J Antimicrob Chemother 2011; 66: 2675-2677.
54) Brinkman MB, Fan K, Shiveley RL, Van Anglen LJ. Successful treatment of polymicrobial calcaneal osteomyelitis with telavancin, rifampin, and meropenem. Ann Pharmacother 2012; 46: e15.
55) Bouza E, Valerio M, Soriano A, Morata L, Carus EG, Rodríguez-González C, Hidalgo-Tenorio MC, Plata A, Muñoz P, Vena A; DALBUSE Study Group (Dalbavancina: Estudio de su uso clinico en España). Dalbavancin in the treatment of different gram-positive infections: a real-life experience. Int J Antimicrob Agents 2018; 51: 571-577.
56) Li J, Zhao QH, Huang KC, Li ZQ, Zhang LY, Qin DY, Pan F, Huang WX. Linezolid vs. vancomycin in treatment of methicillin-resistant staphylococcus aureus infections: a meta-analysis. Eur Rev Med Pharmacol Sci 2017; 21: 3974-3979.
57) Komatsu M, Takahata M, Sugawara M, Takekuma Y, Kato T, Ito M, Abe Y, Irie T, Iwasaki N, Minami A. Penetration of linezolid into rabbit intervertebral discs and surrounding tissues. Eur Spine J 2010; 19: 2149-2155.
58) Metallidis S, Nikolaidis J, Lazaraki G, Koumentaki E, Gogou V, Topsis D, Nikolaidis P, Charokopos N, Theodoridis G. Penetration of linezolid into sternal bone of patients undergoing cardiopulmonary bypass surgery. Int J Antimicrob Agents 2007; 29: 742-744.
59) Kutscha F, Hebler U, Muhr G, Koller M. Linezolid penetration into bone and joint tissues infected with methicillin-resistant staphylococci. Antimicrob Agents Chemother 2003; 47: 3964-3966.
60) Lu PL, Wang JT, Chen CJ, Chen WC, Chen TC, Hwang YC, Chang SC. Compassionate use of linezolid for adult Taiwanese patients with bone and joint infections. Chemotherapy 2010; 56: 429-435.
61) Legout L, Valette M, Dezeque H, Nguyen S, Lemaire X, Loïez C, Caillaux M, Beltrand E, Dubreuil L, Yazdanpanah Y, Migaud H, Senneville E. Tolerability of prolonged linezolid therapy in bone and joint infection: protective effect of rifampicin on the occurrence of anaemia. J Antimicrob Chemother 2010; 65: 2224-2230.
62) Rao N, Hamilton CW. Efficacy and safety of linezolid for gram-positive orthopedic infections: a prospective case series. Diagn Microbiol Infect Dis 2007; 59: 173-179.
63) Aneziokoro CO, Cannon JP, Pachucki CT, Lentino JR. The effectiveness and safety of oral linezolid for the primary and secondary treatment of osteomyelitis. J Chemother 2005; 17: 643-650.
64) Bassetti M, Vitale F, Melica G, Righi E, Di Biagio A, Molfetta L, Pipino F, Cruciani M, Bassetti D. Linezolid in the treatment of gram-positive prosthetic joint infections. J Antimicrob Chemother 2005; 55: 387-390.
65) Howden BP, Ward PB, Charles PG, Korman TM, Fuller A, du Cros P, Grabsch EA, Roberts SA, Robson J, Read K, Bak N, Hurley J, Johnson PD, Morris AJ, Mayall BC, Grayson ML. Treatment outcomes for serious infections caused by methicillin-resistant Staphylococcus aureus with reduced vancomycin susceptibility. Clin Infect Dis 2004; 38: 521-528.
66) Rao N, Ziran BH, Hall RA, Santa ER. Successful treatment of chronic bone and joint infections with oral linezolid. Clin Orthop Relat Res 2004; 427: 67-71.
67) Rayner CR, Baddour LM, Birmingham MC, Norden C, Meagher AK, Schentag JJ. Linezolid in the treatment of osteomyelitis: results of compassionate use experience. Infection 2004; 32: 8-14.
68) Razonable RR, Osmon DR, Steckelberg JM. Linezolid therapy for orthopedic infections. Mayo Clin Proc 2004; 79: 1137-1144.
69) Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: a retrospective survey. Clin Infect Dis 2006; 43: 180-187.

70) Wu VC, Wang YT, Wang CY, Tsai IJ, Wu KD, Hwang JJ, Hsueh PR. High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. Clin Infect Dis 2006; 42: 66-72.
71) Palenzuela L, Hahn NM, Nelson RP Jr, Arno JN, Schobert C, Bethel R, Ostrowski LA, Sharma MR, Datta PP, Agrawal RK, Schwartz JE, Hirano M. Does linezolid cause lactic acidosis by inhibiting mitochondrial protein synthesis? Clin Infect Dis 2005; 40: 113-116.
72) Gandelman K, Zhu T, Fahmi OA, Glue P, Lian K, Obach RS, Damle B. Unexpected effect of rifampin on the PK of linezolid: in silico and in vitro approaches to explain its mechanism. J Clin Pharmacol 2011; 51: 229-236.
73) Ract P, Piau-Couapel C, Compain F, Auzou M, Michon J, Cattoir V. In vitro activity of tedizolid and comparator agents against gram-positive pathogens responsible for bone and joint infections. J Med Microbiol 2017; 66: 1374-1378.
74) Vaudaux P, Francois P, Bisognano C, Schrenzel J, Lew DP. 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: 1503-1509.
75) Shirtliff ME, Calhoun JH, Mader JT. Gatifloxacin efficacy in treatment of experimental methicillin-sensitive Staphylococcus aureus-induced osteomyelitis in rabbits. Antimicrob Agents Chemother 2002; 46: 231-233.
76) Metzler K, Hansen GM, Hedlin P, Harding E, Drlica K, Blondeau JM. Comparison of minimal inhibitory and mutant prevention drug concentrations of 4 fluoroquinolones against clinical isolates of methicillin-susceptible and -resistant Staphylococcus aureus. Int J Antimicrob Agents 2004; 24: 161-167.
77) Blumberg HM, Rimland D, Carroll DJ, Terry P, Wachsmuth IK. Rapid development of ciprofloxacin resistance in methicillin-susceptible and-resistant Staphylococcus aureus. J Infect Dis 1991; 163: 1279-1285.
78) San Juan R, Garcia-Reyne A, Caba P, Chaves F, Resines C, Llanos F, López-Medrano F, Lizasoain M, Aguado JM. Safety and efficacy of moxifloxacin monotherapy for treatment of orthopedic implant-related staphylococcal infections. Antimicrob Agents Chemother 2010; 54: 5161-5166.
79) Kim BN, Kim ES, Oh MD. Oral antibiotic treatment of staphylococcal bone and joint infections in adults. J Antimicrob Chemother 2014; 69: 309-322.
80) Kandemir O, Oztuna V, Colak M, Akdag A, Camdeviren H. Comparison of the efficacy of tigecycline and teicoplanin in an experimental methicillin-resistant Staphylococcus aureus osteomyelitis model. J Chemother 2008; 20: 53-57.
81) Yin LY, Lazzarini L, Li F, Stevens CM, Calhoun JH. Comparative evaluation of tigecycline and vancomycin, with and without rifampicin, in the treatment of methicillin-resistance Staphylococcus aureus experimental osteomyelitis in a rabbit model. J Antimicrob Chemother 2005; 55: 995-1002.
82) Rodvold KA, Gotfried MH, Cwik M, Korth-Bradley JM, Dukart G, Ellis-Grosse EJ. Serum, tissue, and body fluid concentrations of tigecycline after a single 100 mg dose. J Antimicrob Chemother 2006; 58: 1221-1229.
83) Vergidis P, Schmidt-Malan SM, Mandrekar JN, Steckelberg JM, Patel R. Comparative activities of vancomycin, tigecycline and rifampin in a rat model of methicillin-resistant Staphylococcus aureus osteomyelitis. J Infect 2015; 70: 609-615.
84) Prasad P, Sun J, Danner RL, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012; 54: 1699-1709.
85) Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011; 66: 1963-1971.
86) Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? Eur J Clin Microbiol Infect Dis 2009; 29: 127-142.
87) Van Bambeke F. Lipoglycopeptide Antibacterial Agents in gram-Positive Infections: A Comparative Review. Drugs 2015 Dec; 75: 2073-2095.
88) Galanakis N, Giamarellou H, Moussas T, Dounis E. Chronic osteomyelitis caused by multi-resistant gram-negative bacteria: evaluation of treatment with newer quinolones after prolonged follow-up. J Antimicrob Chemother 1997; 39: 241-246.
89) Barberán J, Gomis M, Sánchez B, Hernández-Salván J, García Del Salto L, Carroquino G, González F, Hernández M. Cefepime in the treatment of osteomyelitis caused by gram negative bacilli. Rev Esp Quimioter 2000; 13: 366-373.
90) Widmer AF, Wiestner A, Frei R, Zimmerli W. Killing of nongrowing and adherent Escherichia coli determines drug efficacy in device-related infections. Antimicrob Agents Chemother 1991; 35: 741-746.
91) Legout L, Senneville E, Stern R, Yazdanpanah Y, Savage C, Roussel-Delvalez M, Rosele B, Migaud H, Mouton Y. Treatment of bone and joint infections caused by gram-negative bacilli with a cefepime-fluoroquinolone combination. Clin Microbiol Infect 2006; 12: 1030-1033.
92) Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. J Antimicrob Chemother 2003; 51: 1261-1268.
93) Tascini C, Gemignani G, Palumbo F, Leonildi A, Tedeschi A, Lambelet P, Lucarini A, Piaggesi A, Menichetti F. Clinical and microbiological efficacy of colistin therapy alone or in combination as treatment for multidrug resistant Pseudomonas aeruginosa diabetic foot infections with or without osteomyelitis. J Chemother 2006; 18: 648-651.
94) Rod-Fleury T, Dunkel N, Assal M, Rohner P, Tahintzi P, Bernard L, Hoffmeyer P, Lew D, Uçkay I. Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience. Int Orthop 2011; 35: 1725-1731.
95) Stengel D, Bauwens K, Sehouli J, EkkernkampA, Porzsolt F. Systematic review and meta-analysis of antibiotic therapy for bone and joint infections. Lancet Infect Dis 2001; 1: 175-188.

96) Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? Int J Infect Dis 2005; 9: 127-138.
97) Nowak MA, Winner JS, Beilke MA. Prolonged oral antibiotic suppression in osteomyelitis and associated outcomes in a Veterans population. Am J Health Syst Pharm 2015; 72(23 Suppl): S150-155.
98) Zuluaga AF1, Galvis W, Saldarriaga JG, Agudelo M, Salazar BE, Vesga O. Etiologic diagnosis of chronic osteomyelitis: a prospective study. Arch Intern Med 2006; 166: 95-100.
99) Jiang N, Ma YF, Jiang Y, Zhao XQ, Xie GP, Hu YJ, Qin CH, Yu B. Clinical characteristics and treatment of extremity chronic osteomyelitis in southern China: a retrospective analysis of 394 consecutive patients. Medicine (Baltimore) 2015; 94: e1874.