Curr Infect Dis Rep (2012) 14:566–575
DOI 10.1007/s11908-012-0286-0

Chronic Osteomyelitis

Ilker Uçkay · Kheeldass Jugun · Axel Gamulin · Joe Wagener · Pierre Hoffmeyer · Daniel Lew

Published online: 29 July 2012

Abstract Chronic osteomyelitis is a multifaceted bacterial infection with common features. It absolutely requires surgery for remission. The duration and form of concomitant administration of antibiotic agents for adult patients is still based on expert opinion. The traditional recommendation of 6–12 weeks of antibiotic therapy, where, for at least the first 2–6 weeks, antibiotics should be administered intravenously, is more and more challenged in favor of an oral antibiotic treatment with selected agents from the start. There is no evidence that the total duration of antibiotic therapy for more than 4–6 weeks improves outcome, when compared with shorter regimens. Hopefully, the future will show randomized trials in the adult population, allowing optimal timing of surgical and medical therapy and sparing of unnecessary prescription, with concomitant development of antibiotic resistance. External advice from an expert team with combined surgeons and infectious disease physicians may help to reduce antibiotic consumption in a cost-effective way.

I. Uçkay · K. Jugun · A. Gamulin · J. Wagener · P. Hoffmeyer
Orthopedic Surgery Service, Geneva University Hospitals &
Faculty of Medicine, University of Geneva,
Geneva, Switzerland

I. Uçkay · D. Lew
Service of Infectious Diseases, Geneva University Hospitals &
Faculty of Medicine, University of Geneva,
Geneva, Switzerland

I. Uçkay (✉)
Orthopaedic Surgery Service, Service of Infectious Diseases,
Geneva University Hospitals,
4, Rue Gabrielle Perret-Gentil,
1211 Geneva 14, Switzerland
e-mail: ilker.uckay@hcuge.ch

Keywords Osteomyelitis · Surgery · Antibiotic therapy · Duration · Penetration · Recurrence

Introduction

Chronic bone infection requires combined surgical and medical treatment. It demands long-lasting antibiotic treatments [1], which leads to a high burden on patients and hospitals in terms of morbidity and additional costs [2]. Various reports indicate a minimal cost of $15,000 and a median 2-week prolongation of hospital stay [3]. A persistent mechanic disablement can be witnessed among patients, which is often underreported.

In contrast to other fields of infectiology, the adequate administration route and duration of antibiotic agents in chronic osteomyelitis are not based on randomized trials or other forms of evidence. They rely on expert opinion and some indirect information from animal studies or in vitro experiments. Moreover, many surgeons and physicians tend to administer antimicrobials for longer periods, in order to do something to prevent recurrences, even if their approaches are not supported by expert opinion. These excesses probably further contribute to the emergence and spread of multiresistant pathogens [4]. Traditionally, a 6- to 12-week course of antibiotic therapy is recommended [4, 5•] in association with surgery, where antibiotics are given intravenously for the first 2–4 weeks. In contrast, recent years have seen ongoing research to reduce and simplify the antibiotic treatment of osteomyelitis, especially among the pediatric population [6••].

This review gives an overview of and focuses on new insights into the antibiotic treatment of chronic osteomyelitis. Special features such as pathogenesis or diagnosis,

prevention [4], implant-related bone infections, osteomyelitis accompanying septic arthritis, vertebral spondylodiscitis, mandibular osteomyelitis, tuberculosis, fungal bone infections, and pediatric acute osteomyelitis are exempt or only very briefly mentioned.

Definition and Microbiology

Osteomyelitis is an infection that can be limited to a single portion of bone or can involve several regions, such as marrow, cortex, periosteum, and surrounding soft tissue [2]. Strictly speaking, osteomyelitis implicates affection of bone and marrow. The literature lacks an internationally accepted definition of chronic osteomyelitis [1]. As for any infection, *acute*, *subacute*, and *chronic* [2] are the headings of big groups [7] but are not very useful in clinical practice. A commonly accepted definition requires a minimal symptom duration of 6 weeks to 3 months. Several surgical classifications have been proposed. Among them, the Cierny–Mader classification [8] for long-bone osteomyelitis or the PEDIS classification for diabetic foot osteomyelitis are the most frequently reported. Generally, surgeons understand chronic osteomyelitis as an infection requiring surgery, with already established sequestra or bone deformities.

Infection is almost exclusively of bacterial origin and is much less often due to fungi (intravenous drug abusers [9] or skull osteomyelitis [10]) or parasites (e.g., echinococcosis). Among all bacteria and types of osteomyelitis except for the jaw, *Staphylococcus aureus* dominates [2, 11•], followed by streptococci and Gram-negative pathogens [12]. In sickle-cell disease-associated bone necrosis and subsequent osteomyelitis [13], the hallmark is Gram-negative pathogens [14]—for example, *Salmonella* spp [2]. Polymicrobial infection is frequent in trauma [15] and long-lasting ulcerations [16]. Anaerobes are rare [17], and coagulase-negative staphylococci are retrieved almost exclusively in implant-related osteomyelitis [11•].

Pathogenesis

Bacteria adhere to bone matrix via receptors to fibronectin and other structural proteins by developing a biofilm [11•, 18]. Biofilms are the hallmark of implant-related osteomyelitis but are also important in the absence of a foreign body [19, 20••]. In biofilms, pathogens undergo complex metabolic changes and become less susceptible not only to the immune system, but also to antibiotics [21]. For cell-wall-active antibiotics to be effective in biofilms, 100 to 1,000 times the standard concentration is often required [22]. Additionally, the biofilm inhibits the activity of mononuclear cells, T and B lymphocytes, and chemotactic responsiveness, thus adversely acting on both cytotoxic and humoral defense responses [23]. On a macroscopic level, patchy ischemic bone necrosis occurs when the inflammation occludes vascular tunnels. Segments of bone devoid of blood supply can become separated and are called *sequestrae* [2]. At the infarction edge, there is reactive hyperemia with increased osteoclastic activity [2]. This activity produces bone loss. Meanwhile, bone apposition occurs—in some cases, exuberantly—causing periosteal apposition and new bone formation, named *involucrae* [2].

Diagnosis

Clinical signs and standard radiographs are suggestive for diagnosis, but no noninvasive test can definitively exclude osteomyelitis [24]. The ultimate proof requires growth of the same pathogens in several, at least two, bone samples [11•]. Bacteremic disease is rare, and the use of serum antistreptolysin-O-titers for serological diagnosis of invasive β-hemolytic streptococci is seldom reliable [25]. The value of pathogen identification with bone surface swabs is far from being excellent [26, 27]. Radiological signs in standard X-rays are numerous, but only very few are suggestive of osteomyelitis: sinus tract or the radiological evidence of sequesters and involucres.

Treatment

Chronic osteomyelitis is a surgical disease [2, 28]. For chronic osteomyelitis, antibiotics alone are very rarely successful, because of the biofilm and sequester formation, which they cannot penetrate, or only very little. Without adequate debridement, chronic osteomyelitis does not respond to antibiotic regimens, no matter what the antibiotic choice or the duration of therapy is. Antibiotic administration without surgery may eradicate infection only for some exceptions: childhood osteomyelitis, spondylodiscitis, tuberculous osteomyelitis, and in selected cases, diabetic toe osteomyelitis. On the other hand, lack of systemic antibiotics [29] yields higher failure rates, highlighting an independent benefit of concomitant antibiotic therapy.

Surgical Treatment

The optimal management includes sequestrectomy, resection of scarred and infected bone as well as soft tissue [2, 8], obliteration of dead space, appropriate bone mechanical stability, adequate soft-tissue coverage, and restoration of an effective blood supply [2]. The debridement is usually aggressive and as complete as possible [30]. If the stability

of the bone is compromised, a two-stage procedure might be required [31]. The first stage consists of extensive debridement, dead space management with antibiotic-containing beads or cement (Fig. 1), bone stabilization with external fixation, and coverage with dressings. After 2–3 weeks of antibiotic treatment comes the second stage: new debridement, removal of the beads or cement, filling in of the dead space with bone graft, bone stabilization with internal fixation (plate and/or intramedullary nail), and soft-tissue coverage. A small dead space is left unchanged if the soft-tissue coverage is good. Large dead spaces are filled to reduce the likelihood of continued infection and stability loss. If a cavity cannot be filled by surrounding soft tissue, a local muscle flap [17] or free tissue transfer obliterates the space. Autologous bone grafts usually enhance stability after 6–8 weeks. The Ilizarov technique may bridge bone defects as long as 15 cm by continuous traction that can be started 10 days after implantation of the device. Coverage with a vacuum-assisted closure dressing is discouraged by some surgeons or simply performed by others [32]. Amputation is infrequent for long-bone osteomyelitis [33], in contrast to the diabetic foot.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy consumes very substantial resources [34]. It is said to provide oxygen to promote collagen production, angiogenesis, and osteogenesis [24, 35]. Several authors have suggested that adjunctive hyperbaric oxygen might be useful in human chronic osteomyelitis, even if the results are not consistent [24].

Antibiotic Treatment

Whereas expert opinion and scientific evidence are rich for hematogenous childhood [6••] or implant-related osteomyelitis [36], the optimal antibiotic duration and administration form postdebridement for implant-free osteomyelitis among adults remains unknown [1, 2, 15, 37••]. Different case series express different durations without comparison within [1, 15, 37••] and between the reports, and international consensus guidelines are lacking [1].

Parenteral Antibiotic Therapy

In former times, experts usually recommended an intravenous (IV) therapy for 4 [28] to 6 weeks [2, 15, 38, 39], followed by an oral course of additional weeks or months [40]. The rationale for a prolonged IV course was elevated serum concentrations, according to expert opinion. Today, this opinion has rather switched for IV treatment during the initial 2 weeks [41]. Without doubt, bone penetration of antibiotic agents in parenteral administration is good and bioavailability per definition 100 % [42]. At the same time, IV medication should be limited as far as possible to save unnecessary costs, prevent catheter-related complications, and increase patient and nursing comfort. The estimated proportion of complications attributed to prolonged IV course ranges around 15 % [37••, 39]. Recent retrospective data suggest that regimens with an early switch to oral antibiotics are as effective as prolonged parenteral regimens [10, 20••, 43]. A Cochrane review in 2009 included eight trials comparing oral versus IV antibiotics for chronic osteomyelitis in adults. There was no statistically significant difference in the remission rate at 12 months follow-up, but the rate of adverse events was significantly higher with IV administration [37••]. The authors of this article performed a retrospective analysis at their center, with a minimal follow-up of 2 years after treatment. Among 49 episodes of implant-free chronic osteomyelitis, 20 % recurred. However, in multivariate logistic regression analysis, 1 week of IV therapy had the same remission as 2–3 weeks or more than 3 weeks [5•]. Several antibiotic agents proved clinical efficacy upon oral intake: quinolones [12,

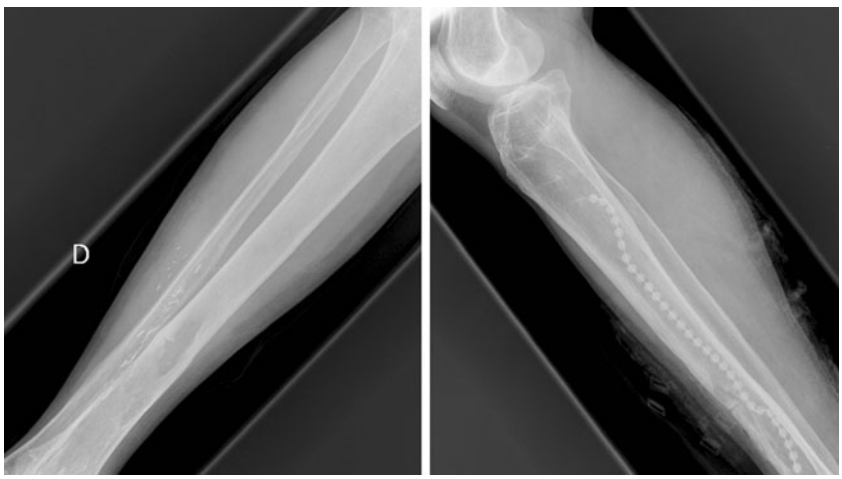

Fig. 1 Left: Standard X-ray of a chronic osteomyelitis of the tibia. The bone is irregular in shape with involvement of the intramedullary canal and cortical extension. Right: Lateral view of the same case, showing cortical fenestration and insertion of gentamicin beads for treatment

44], linezolid, metronidazole, clindamycin, and fusidic acid combined with rifampin [20••, 38]. These drugs have an oral bioavailability of over 90 % [45•].

Duration of Antibiotic Therapy

As a general principle, the duration of antibiotic administration does not depend on the pathogen, with few exceptions: osteomyelitis with pathogens for which the literature provides long-lasting antibiotic treatments (tuberculosis [2, 46], other mycobacteria such as in buruli ulcer [47], fungi [9], Q fever [48], nocardiosis [49], or brucellosis [50]).

Total duration of antibiotic treatment, concomitant to surgery, can probably be limited to 6 weeks [20••]. To our best knowledge, only one paper from 1985 really attributes an unacceptable high risk of treatment failure, when antibiotics are administered for less than 4 weeks [51]. Besides this exception, there are no clinical studies or documented records indicating the superiority of the 4- to 6-week course over shorter durations [5•, 15, 20••, 52]. Nonrandomized trials of longer courses of intravenous or oral antibiotics (6 months or more) do not suggest any improvement, as compared with 6 weeks of therapy [20••, 24]. As a clinical example, Eyichukwu et al. reported arrest of chronic osteomyelitis after surgery and a short-term sensitivity-based IV course of 2–3 days, followed by oral administration [53]. In their recent review regarding duration of antibiotic treatment for osteomyelitis, Haidar et al. listed small individual reports in animals and humans that obtained remissions with antibiotic durations ranging from 1 to 4 weeks [15]. In the aforementioned retrospective analysis in Geneva among 49 patients with chronic osteomyelitis, 4 weeks of total antibiotic treatment had the same outcome as 4–6 weeks, 7–12 weeks, or more than 12 weeks [5•]. Unfortunately, in today's practice, long post-surgical oral durations are still frequent [54, 55], ranging from 6 [1, 44] to 10 [53] months or 2 years [1].

Choice of the Antimicrobial Agent

Antimicrobials are based on the susceptibility of the isolated pathogen, bone penetration, and oral bioavailability (Table 1). Single-agent antibiotic therapy is usually adequate, and better pharmacokinetic and -dynamic properties in vitro do not need to show a direct correlation with clinical outcome.

Ideally, the agent should have bactericidal activity against slow-growing and biofilm-producing bacteria. Rifampin fulfils these criteria for staphylococci, although the classical indication for combined rifampin is staphylococcal implant infection. Nevertheless, rifampin can also be used for implant-free osteomyelitis [20••]. It can penetrate phagocytes and kill intracellular bacteria [56] but may lead to the rapid emergence of rifampin-resistant staphylococci during monotherapy [11•]. Different antibiotics, such as co-trimoxazole, fusidic acid, tigecycline, daptomycin, linezolid, dalbavancin, quinupristin/dalfopristin, minocycline, and quinolones, have been used in combination as a panel [11•, 20••]. The efficacy of many of these possible combinations is not established in vivo. For instance, the combination of rifampin with lincosamides (clindamyin [57], macrolides) or moxifloxacin is uncertain in humans [11•]. Doses of rifampin ranging from 1×600 mg [20••] to 2×450 mg to 2×600 mg are used in routine practice in several parts of the world. In contrast to rodents, in which higher doses yielded some better cure rates, no prospective randomized trials exist in humans. The authors of this article and other experts [20••] consider 600 mg daily as sufficient.

Beta-lactam antibiotics can be used intravenously. As a group, this large class of antibiotics has one important drawback—that is, low oral bioavailability, together with a low intraosseous penetration [38, 58].

Since the bone penetration of vancomycin is only about 15 %–30 % of the serum concentration, minimal serum through levels of 20–25 mg/ml is believed to treat bone infections best [59]. In continuous perfusion, the changes in serum concentrations are much lower than in intermittent application. The target concentrations are achieved more quickly with fewer adverse drug effects [59]. However, continuous perfusion does not guarantee a better outcome in term of remission [60]. Teicoplanin is available in Europe and elsewhere, but not in the United States. For bone infections, a high dose of serum concentrations appears necessary, but the ideal serum through level or daily dose remains unknown. LeFrock et al. used doses of 6–12 mg/kg to treat bone and joint infections [61].

Daptomycin depolarizes membranes and yields a rapid, dose-dependent bactericidal effect. It is available only in parenteral form and is administered once a day at a dose of 6–8 mg/kg. This makes it suitable for an outpatient treatment. Clinicians should keep in mind that emergence of a daptomycin-resistant *S. aureus* isolate during treatment of initially daptomycin-susceptible MRSA osteomyelitis has been described [62]. Trials with higher doses up to 10 mg/kg are ongoing to overcome this problem.

Tigecycline belongs to the glycylcyclines, a further development of tetracycline antibiotics with a five times higher affinity to the target. It is available only in parenteral form: charging dose of 100 mg, followed by 50 mg bid intravenously. Today, it has to be considered as an experimental drug for osteo-articular infections [63].

Aminoglycosides are less active in synovial fluid or in bone [64]. Furthermore, staphylococcal small-colony variants, a hallmark of chronic pretreated osteo-articular *S.*

Table 1 Antibiotic treatment of chronic implant-free osteomyelitis (concomitant to surgery if no surgical removal *in toto*; personal suggestions)

Parenteral treatment				Oral treatment		
	Antibiotic	Alternatives	Duration	Antibiotic	Alternatives	Duration[p]
Methicillin-resistant staphylococci	Vancomycin[a]	Teicoplanin[c]	0–2 weeks	Fusidic acid[g] + rifampin[b]	Ciprofloxacin[h] + rifampin[b]	6–12 weeks
		Daptomycin[n]	0–2 weeks		Levofloxacin[i] + rifampin[b]	6–12 weeks
		Tigecycline[d]	0–2 weeks		Doxycyclin[k] + rifampin[b]	6–12 weeks
		Linezolid[e]	0–2 weeks		Minocyclin[l] + rifampin[b]	6–12 weeks
		Ceftobripole[f]	0–2 weeks		Cotrimoxazole[m] + rifampin[b]	6–12 weeks
Methicillin-sensitive staphylococci and other Gram-positives	Cephalosporins of 1st or 2nd generation,	Vancomycin[a]	0–2 weeks	Clindamycine[p]	Ciprofloxacin[h] + rifampin[b]	6–12 weeks
		Daptomycin[n]	0–2 weeks		Levofloxacin[i] (+ rifampin[b])	6–12 weeks
		Penicillins	0–2 weeks		Cotrimoxazole[m] + rifampin[b]	6–12 weeks
Gram-negatives	Ceftriaxon	Ceftriaxone	0–2 weeks		Ciprofloxacin[h]	6–12 weeks
		Ceftazidime	0–2 weeks		Levofloxacin[i]	6–12 weeks
		Cefepime	0–2 weeks			
Anaerobes	Amoxicillin-clavulanate	Carbapenems	0–2 weeks	Metronidazole[q]	Clindamycine[p]	6–12 weeks

[a] Vancomycin: 2×15 mg/kg iv or 30 mg/kg/d in continuous infusion. Targeted serum vancomycinemia in steady state: ~25 mg/L

[b] Rifampin: 600–1,200 mg/d. Parenteral medication not necessary. Always in combination, never alone (development of resistance)

In absence of implants, rifampin is not indicated, but may be used in combination therapy because of good bone penetration

[c] Teicoplanin: 1st day 2×400 mg intravenously. From 2nd day 1×400 mg iv. It can also be given by intramuscular route

[d] Tigecycline: 100 mg iv once, thereafter 2×50 mg/d iv. Mostly experimental so far

[e] Linezolid: 2×600 mg/d. In non-bacteremic cases, linezolid can be given orally. Be aware of interactions with MAO-inhibitors, myelosuppression, and polyneuropathy

[f] Ceftobripole: 2–3×500 mg/d. No studies for osteomyelitis thus far

[g] Fusidic acid: 3×500 mg/d. Always in combination (possible development of resistance during monotherapy)

[h] Ciprofloxacin: 2×500 mg/d in combination, 2×750 mg in monotherapy

[i] Levofloxacin: 2×500 mg/d

[k] Doxycyclin: 2×100 mg/d

[l] Minocyclin: 2×100 mg/d

[m] Cotrimoxazole: 2 double-strength tablets (800 mg trimethroprim, 160 mg sulfadiaxozide) per day. May have failure when high inoculums. Eventually 3 × double-strength tablets per day

[n] Daptomycine: 6–10 mg/kg/d once daily. Few data on human osteo-articular infections available

[p] Clindamycine: 3×600 mg/d

[q] Metronidazole: 3×500 mg/d

aureus infections, are generally resistant to aminoglycosides [64]. However, in desperate situations and in low-income countries, aminoglycosides might be an option.

Linezolid inhibits ribosomal protein synthesis and can be administered parenterally or orally at a dose of 600 mg bid. It is bacteriostatic with no cross-resistance to other antibiotics and is essentially anti-Gram-positive. Due to its excellent bioavailability of 100 %, it is a good choice for outpatient treatments [65]. Nevertheless, it also features some inconveniences: Besides an expensive price, it is associated with reversible bone marrow suppression, particularly thrombopenia, for an administration of more than 2 weeks. Optic neuropathy and nonreversible peripheral neuropathy have been reported in 2 % −4 % [66] of patients with prolonged administration. A severe serotonin syndrome in co-medication with certain antidepressive drugs, such as monoamine oxidase inhibitors, has been described [67].

Co-trimoxazole is an inexpensive bactericidal folate antagonist. Clinical experience shows that this molecule can heal small soft-tissue infections [68]. However, it has not been FDA-approved for severe *S. aureus* infections [69]. One reason for failure in severe infections might be the amount of thymidine released from damaged host tissues and bacteria, a concept strengthened by the fact that *S. aureus* thermonuclease releases thymidine from DNA. Thymidine antagonizes the antistaphylococcal effects of both trimethoprim and sulfamethoxazole, the two compounds of co-trimoxazole. Thus, failure with co-trimoxazole may well

depend on the amount of tissue damage and organism burden [70].

Tetracyclines (doxycycline and minocycline; both 100 mg bid) are lipophilic, facilitating the passage into tissues. Evidence exists essentially for skin and soft-tissue infections, but unfortunately not much for osteomyelitis. Tetracyclines are often combined with rifampin, although firm data are lacking [71, 72].

Oral fusidic acid 500 mg tid has demonstrated efficacy in chronic osteomyelitis [73]. Most experts [74] do not recommend monotherapy, because of development of resistance [75]. The time delay under current therapy until the appearance of resistance is unknown and might be variable. The antibiotic can be combined with rifampin [76]. Fusidic acid is available in some (not all) European countries, but not in the United States [38].

Streptogramins such as quinupristin-dalfopristin (IV) or pristinamycin (oral) inhibit protein synthesis by binding to bacterial ribosomes. Quinupristin-dalfopristin administration requires central venous access and dextrose infusion [38] and is not frequently used.

For anaerobic, streptococcal, and staphylococcal clindamycine-sensitive osteomyelitis, bacterial protein synthesis inhibition by clindamycin 600–900 mg tid is an option [20••]. The clinical efficacy of clindamycin in bone infection can be explicated by its excellent penetration despite its classification as a bacteriostatic agent [45•].

Although staphylococci may be susceptible to fosfomycin and chloramphenicol and despite their excellent tissue penetration, these antibiotics have not been much approved for osteo-articular infections [77]. Physicians fear agranulocytosis under chloramphenicol medication. For anaerobic osteomyelitis, metronidazole is the drug of choice [14], as are quinolones [12, 20••, 78] for Gram-negative infection. Quinolones are the only available class for Gram-negative infections in oral form and are, therefore, precious. *Pseudomonas aeruginosa* and other nonfermenting Gram-negative rods may rapidly develop resistance in monotherapy. Therefore, a combination with another parenteral drug or prolonged IV treatment in pseudomonal osteomyelitis would be wise, but no antibiotic treatment adapted for this situation has been studied, to the best of our knowledge. Of note, the optimal oral dose for ciprofloxacin for bone and synovial infections is set at 750 mg bid [1, 20••, 37••, 44, 79••, 80] for patient with a good renal function. Ciprofloxacin can "cure" staphylococcal osteomyelitis also in monotherapy [20••, 44], but probably fewer streptococcal infections. Indeed, a meta-analysis including seven studies and 411 patients reported equivalence in the remission rates of osteomyelitis treated with quinolones, as compared with beta-lactam antibiotics [12]. We would preserve this medication for combined treatment with rifampin or for resistant Gram-negative pathogens [12].

Local Antibiotic-Releasing Delivery Systems

The ideal local antibiotic delivery system is lacking [81]. Available systems release antibiotics locally at concentrations exceeding up to 1,000 times those of the minimum inhibitory concentrations for the most common pathogens without releasing in the systemic circulation [82]. However, the duration of time over which these antibiotics continue to be active is less certain. Gentamicin, the most frequently used antibiotic compound, may theoretically lead to development of small colony variants [64]. It is unknown whether local antibiotic delivery could be equivalent to systemic antibiotics. Only a few available data suggest an equivalent remission rate up to 78 % in osteomyelitis patients treated with beads alone [83]. The major disadvantage of local beads is the presumed need for surgical removal [82].

Outcomes and Variables Associated with Treatment Failures

Recurrences of osteomyelitis after several years, if not decades, have been reported [84]. Many experts advocate that if the bone is infected, it may remain infected throughout life and even beyond, unless an amputation is performed. Some authors suggest that "arrest" or "remission" is a more appropriate term than "cure" for defining the outcome in chronic osteomyelitis [24]. In general, remission rates for osteomyelitis oscillate from 40 % [80, 85] to a peak of success around 80 % [1, 37••]. Of note, high remission reports are often seen in short follow-up times [86] or among children [33].

In contrast to arthroplasty infection [87], no such epidemiological studies exist regarding association with recurrence risk for inplant-free osteomyelitis. Inadequate debridement may be the most important reason for failure [40, 88]. Staphylococcal small-colony variants are further considered as risk [2, 64]. Previously infected bone must be considered a lifetime focus of diminished resistance, and thus former osteomyelitis should be considered a risk factor for a second episode by another pathogen at the same site, due to altered bone surfaces [84]. Further reported variables associated with treatment failure are smoking [17, 89], older age [89], distal tibia osteomyelitis [17], or duration of discharge before treatment [17, 88].

It is an unresolved topic if the pathogen itself increases the likelihood of treatment failure in implant-free osteomyelitis. Sparse and heterogeneous data suggest that *P. aeruginosa* might be more associated with failures than *S. aureus* [20••, 90], but this needs confirmation.

One very rare, but potentially fatal, late-term (after decades) complication of untreated chronic osteomyelitis is squamous cell carcinoma [91], also called Marjolin's ulcer [91]. The physiopathological mechanism of this transformation is largely unknown [91], and overall incidence is believed to be around 0.2 % among all chronic cases of osteomyelitis [91].

Special Features

Diabetic Foot Osteomyelitis

Clinicians must recognize main differential diagnoses of diabetic foot osteomyelitis, which are the Charcot foot [19], gout, and inflammation due to ischemia itself [19, 92•]. In perforating ulcers, there is an underlying osteomyelitis in about 15 % [2] to 20 % [93, 94], especially if the wound extends to bone and joints. According to an international expert panel, no significant differences in outcome are associated with any particular treatment strategy [92•]. There are no data supporting the superiority of any particular delivery route of systemic antibiotics or the optimal therapy duration [92•]. Bioavailable oral antibiotics are sufficient in most mild and moderate osteomyelitis [92•]. Aerobic Gram-positive cocci (especially *S. aureus*) are predominant [95]. Thus, therapy aimed solely at aerobic Gram-positive cocci may be sufficient for mild-to-moderate infections in patients who have not recently received antibiotic therapy [92•]. Patients with chronic wounds or those who have recently received antibiotic therapy may also be infected with Gram-negative rods. Broad-spectrum empirical therapy takes part of severe infections. In severe diabetic foot infections, antibiotics are given initially intravenously to achieve maximal tissue concentrations in an area already compromised by arteriopathy, although no evidence for a superiority of IV medication exists [92•, 94]. Expert suggestions for the duration of antibiotic therapy for acute osteomyelitis are 6 weeks [19, 94] and, for chronic infection, are at least 12 weeks [93, 94], if not up to 46 weeks [16, 93]. No available evidence supports the use of hyperbaric oxygen or granulocyte-colony stimulating factors [92•].

There is no scientific evidence that surgical debridement of infected bone is routinely necessary in patients without osseous or articular deformation and pathologic weight charges due to neuropathy [92•, 95], although surgery is very convenient, rapidly healing, and superior in most cases, as compared with conservative approaches. Prolonged courses of oral antibiotics are, moreover, associated with an increased risk of diarrhea caused by *Clostridium difficile* or emergence of multidrug-resistant organisms [96•]. Conservative success rates have been cited as 75 % [93] and as 77 % [95] over a median period of follow-up of 2 years [95]. Further research is required to establish the relative importance of surgical or conservative approaches [96•].

Sacral Osteomyelitis

This chronic osteomyelitis is related to decubitus in patients with multiple comorbidities and/or neurologic disorders. It is perhaps the most difficult osteomyelitis to treat, since there is no remission because the reason for chronic osteomyelitis cannot be reversed. In these chronic decubitus patients, the infected sacral bone often cannot be excised, and the patient cannot be improved neurologically. Prevention is of utmost importance. Thorough daily nursing care, avoiding pressure ulcers (position changes, specialized beds), and debridement are the keys to success. In ameliorated cases, plastic surgeons may graft. The ideal duration of antibiotic administration is unknown. Since it is a palliative situation, the authors of this article administer antibiotics for 2–4 weeks. The aim is not to eradicate bone infection but to calm it. Clearly, more research is needed is this field of osteomyelitis.

Conclusion

Chronic osteomyelitis is a multifaceted bacterial infection that requires surgery for treatment. The duration and form of concomitant administration of antibiotic agents are based on expert opinion. The traditional recommendation of 6–12 weeks of antibiotic therapy, of which at least the first 2–6 weeks are intravenous, is more and more challenged in favor of an oral antibiotic treatment with selected agents from the start [20••]. There is no evidence that a total duration of more than 4–6 weeks improves outcome, when compared with shorter regimens. External advice from an infectious diseases physician may help to narrow the initial antibiotic and may further help to reduce antibiotic consumption in a cost-effective way [97]. The future may eventually bring even shorter regimens in adults with selected oral agents, since there is already ongoing research and evidence for pediatric septic arthritis and (acute) osteomyelitis [6••].

Acknowledgments We thank the teams of the Orthopedic and Infectious Diseases Departments of Geneva University Hospitals.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. 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;9:127–38.
2. Lew DP, Waldvogel FA. Osteomyelitis. Lancet. 2004;364:369–79.
3. Whitehouse JD, Friedman ND, Kirkland KB, et al. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. Infect Control Hosp Epidemiol. 2002;23:183–9.
4. Uçkay I, Harbarth S, Peter R, et al. Preventing surgical site infections. Expert Rev Anti Infect Ther. 2010;8:657–70.
5. • Rod-Fleury T, Dunkel N, Assal M, et al. Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience. Int Orthop. 2011;35:1725–31. *Retrospective single-centre study regarding the optimal duration of antibiotic treatment concomitant to surgery in implant-free chronic osteomyelitis. Short regimens do not enhance recurrence risk.*
6. •• Paakkonen M, Peltola H. Antibiotic treatment for acute haematogenous osteomyelitis of childhood: moving towards shorter courses and oral administration. Int J Antimicrob Agents. XXX,38:273–280. *A state-of-the art paper concerning short antibiotic regimens for pediatric cases.*
7. Waldvogel FA, Medoff G, Swartz MN. Treatment of osteomyelitis. N Engl J Med. 1970;283:822.
8. Cierny 3rd G, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. Clin Orthop Relat Res. 2003;414:7–24.
9. Legout L, Assal M, Rohner P, et al. Successful treatment of Candida parapsilosis (fluconazole-resistant) osteomyelitis with caspofungin in a HIV patient. Scand J Infect Dis. 2006;38:728–30.
10. Blyth CC, Gomes L, Sorrell TC, et al. Skull-base osteomyelitis: fungal vs. bacterial infection. Clin Microbiol Infect. 2011;17:306–11.
11. • Uçkay I, Pittet D, Vaudaux P, et al. Foreign body infections due to *Staphylococcus epidermidis*. Ann Med. 2009;41:109–19. *Clinical problems dealing with biofilms in implant-associated infections*.
12. Karamanis EM, Matthaiou DK, Moraitis LI, Falagas ME. Fluoroquinolones versus beta-lactam based regimens for the treatment of osteomyelitis: a meta-analysis of randomized controlled trials. Spine. 2008;33:297–304.
13. Hernigou P, Daltro G, Flouzat-Lachaniette CH, et al. Septic arthritis in adults with sickle cell disease often is associated with osteomyelitis or osteonecrosis. Clin Orthop Relat Res. 2010;468:1676–81.
14. Al-Tawfiq JA. *Bacteroides fragilis* bacteremia associated with vertebral osteomyelitis in a sickle cell patient. Intern Med. 2008;47:2183–5.
15. Haidar R, Der Boghossian A, Atiyeh B. Duration of post-surgical antibiotics in chronic osteomyelitis: empiric or evidence-based? Int J Infect Dis. 2010;14:752–8.
16. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg. 2006;117:212–38.
17. Beals RK, Bryant RE. The treatment of chronic open osteomyelitis of the tibia in adults. Clin Orthop Relat Res. 2005;433:212–7.
18. Ciampolini J, Harding KG. Pathophysiology of chronic bacterial osteomyelitis. Why do antibiotics fail so often? Postgrad Med J. 2000;76:479–83.
19. Hannan CM, Attinger CE. Special considerations in the management of osteomyelitis defects (diabetes, the ischemic or dysvascular bed, and irradiation). Semin Plast Surg. 2009;23:132–40.
20. •• Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012;54:393–407. *Summary of antibiotic administration for osteomyelitis. Favors early switch to oral regimens*.
21. Costerton W, Veeh R, Shirtliff M, et al. The application of biofilm science to the study and control of chronic bacterial infections. J Clin Invest. 2003;112:1466–77.
22. Ceri H, Olson ME, Stremick C, et al. The Calgary Biofilm Device: new technology for rapid determination of antibiotic susceptibilities of bacterial biofilms. J Clin Microbiol. 1999;37:1771–6.
23. Lew D, Schrenzel J, François P, Vaudaux P. Pathogenesis, prevention, and therapy of staphylococcal prosthetic infections. Curr Clin Top Infect Dis. 2001;21:252–70.
24. Calhoun JH, Manring MM. Adult osteomyelitis. Infect Dis Clin North Am. 2005;19:765–86.
25. Uçkay I, Ferry T, Stern R, et al. Use of serum antistreptolysin-O-titers in the microbial diagnosis of orthopedic infections. Int J Infect Dis. 2009;13:421–4.
26. Bernard L, Uçkay I, Vuagnat A, et al. Two consecutive deep sinus tract cultures predict the pathogen of osteomyelitis. Int J Infect Dis. 2009;14:390–3.
27. Mackowiak PA, Jones SR, Smith JW. Diagnostic value of sinus-tract cultures in chronic osteomyelitis. JAMA. 1978;239:2772–5.
28. Parsons B, Strauss E. Surgical management of chronic osteomyelitis. Am J Surg. 2004;188:57–66.
29. Boda A. Antibiotic irrigation-perfusion treatment for chronic osteomyelitis. Arch Orthop Trauma Surg. 1979;95:31–5.
30. Berendt T, Byren I. Bone and joint infection. Clin Med (London, England). 2004;4:510–8.
31. Kınık H, Karaduman M. Cierny-Mader Type III chronic osteomyelitis: the results of patients treated with debridement, irrigation, vancomycin beads and systemic antibiotics. Int Orthop. 2008;32:551–8.
32. Tan Y, Wang X, Li H, et al. The clinical efficacy of the vacuum-assisted closure therapy in the management of adult osteomyelitis. Arch Orthop Trauma Surg. 2011;131:255–9.
33. Beckles VL, Jones HW, Harrison WJ. Chronic haematogenous osteomyelitis in children: a retrospective review of 167 patients in Malawi. J Bone Joint Surg Br. 2010;92:1138–43.
34. Berendt AR. Counterpoint: hyperbaric oxygen for diabetic foot wounds is not effective. Clin Infect Dis. 2006;43:193–8.
35. Andel H, Felfernig M, Andel D, et al. Hyperbaric oxygen therapy in osteomyelitis. Anaesthesia. 1998;53:68–9.
36. Bernard L, Legout L, Zürcher-Pfund L, et al. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. J Infect. 2010;61:125–32.
37. •• Conterno LO, da Silva Filho CR. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev. 2009;3: CD004439. *Metaanalysis regarding antibiotic duration and administration form in adult chronic osteomyelitis*.
38. Mader JT, Shirtliff ME, Bergquist SC, Calhoun J. Antimicrobial treatment of chronic osteomyelitis. Clin Orthop Relat Res. 1999;360:47–65.
39. Matthews PC, Conlon CP, Berendt AR, et al. Outpatient parenteral antimicrobial therapy (OPAT): is it safe for selected patients to self-administer at home? a retrospective analysis of a large cohort over 13 years. J Antimicrob Chemother. 2007;60:356–62.
40. Auh JS, Binns HJ, Katz BZ. Retrospective assessment of subacute or chronic osteomyelitis in children and young adults. Clin Pediatr. 2004;43:549–55.
41. Uçkay I, Lew DP. Infections in skeletal prostheses. In: Lippincott JW, editor. Bennet & Brachman's hospital infections. Philadelphia: Williams & Wilkins; 2007. p. 665–72. 39.
42. Smilack JD, Flittie WH, Williams Jr TW. Bone concentrations of antimicrobial agents after parenteral administration. Antimicrob Agents Chemother. 1976;9:169–71.
43. Daver NG, Shelburne SA, Atmar RL, et al. Oral step-down therapy is comparable to intravenous therapy for *Staphylococcus aureus* osteomyelitis. J Infect. 2007;54:539–44.

44. Dellamonica P, Bernard E, Etesse H, et al. Evaluation of pefloxacin, ofloxacin and ciprofloxacin in the treatment of thirty-nine cases of chronic osteomyelitis. Eur J Clin Microbiol Infect Dis. 1989;8:1024–30.
45. • Toma MB, Smith KM, Martin CA, Rapp RP. Pharmacokinetic considerations in the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis. Orthopedics. 2006;29:497–501. *Pharmacokinetic considerations or oral antibiotics for treatment of osteomyelitis*.
46. Martini M, Adjrad A, Boudjemaa A. Tuberculous osteomyelitis. A review of 125 cases. Int Orthop. 1986;10:201–7.
47. Abgueguen P, Pichard E, Aubry J. Buruli ulcer or *Mycobacterium ulcerans* infection. Med Mal Infect. 2010;40:60–9.
48. Landais C, Fenollar F, Constantin A, et al. Q fever osteoarticular infection: four new cases and a review of the literature. Eur J Clin Microbiol Infect Dis. 2007;26:341–7.
49. Uçkay I, Bouchuiguir-Wafa K, Ninet B, et al. Posttraumatic ankle arthritis due to a novel *Nocardia* species. Infection. 2010;38:407–12.
50. Sürücüoğlu S, El S, Ural S, et al. Evaluation of real-time PCR method for rapid diagnosis of brucellosis with different clinical manifestations. Pol J Microbiol. 2009;58:15–9.
51. Gentry LO. Antibiotic therapy for osteomyelitis. Infect Dis Clin North Am. 1990;4:485–99.
52. Lack W, McKinley T. Marjolin's ulcer: incidental diagnosis of squamous cell carcinoma on hemipelvectomy for recalcitrant pelvic osteomyelitis. Iowa Orthop J. 2010;30:174–6.
53. Eyichukwu GO, Anyaehie UE. Outcome of management of chronic osteomyelitis at National Orthopaedic Hospital, Enugu. Niger J Med. 2009;18:194–8.
54. Uçkay I, Dinh A, Vauthey L, et al. Spondylodiscitis due to *Propionibacterium acnes*: report of twenty-nine cases and a review of the literature. Clin Microbiol Infect. 2010;16:353–8.
55. Salvana J, Rodner C, Browner BD, et al. Chronic osteomyelitis: results obtained by an integrated team approach to management. Conn Med. 2005;69:195–202.
56. Mandell GL. The antimicrobial activity of rifampin: emphasis on the relation to phagocytes. Rev Infect Dis. 1983;5:463–7.
57. Czekaj J, Dinh A, Moldovan A, et al. Efficacy of a combined oral clindamycin-rifampicin regimen for therapy of staphylococcal osteoarticular infections. Scand J Infect Dis. 2011;43:962–7.
58. Uçkay I, Laurent F, Lustig S, et al. Hospital and community-acquired methicillin-resistant *Staphylococcus aureus* bone and joint infections. In: Kolendi CL, editor. Methicillin-resistant *Staphylococcus aureus.* Etiology, at-risk populations and treatment. New York: Nova Science Publishers; 2010. p. 143–209. 4.
59. Vuagnat A, Stern R, Lotthe A, et al. High dose vancomycin for osteomyelitis: continuous vs. intermittent infusion. J Clin Pharm Ther. 2004;29:351–7.
60. Boffi El Amari E, Vuagnat A, Stern R, et al. High versus standard dose vancomycin for osteomyelitis. Scand J Infect Dis. 2004;36:712–7.
61. LeFrock JL, Ristuccia AM, Ristuccia PA, et al. Teicoplanin in the treatment of bone and joint infections. Eur J Surg Suppl. 1992;567:9–13.
62. Marty FM, Yeh WW, Wennersten CB, et al. Emergence of a clinical daptomycin-resistant *Staphylococcus aureus* isolate during treatment of methicillin-resistant *Staphylococcus aureus* bacteremia and osteomyelitis. J Clin Microbiol. 2006;44:595–7.
63. Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis. 2005;41:341–53.
64. Vaudaux P, Kelley WL, Lew DP. *Staphylococcus aureus* small colony variants: difficult to diagnose and difficult to treat. Clin Infect Dis. 2006;43:968–70.
65. Weigelt J, Itani K, Stevens D, et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother. 2005;49:2260–6.
66. Bishop E, Melvani S, Howden BP, et al. Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. Antimicrob Agents Chemother. 2006;50:1599–602.
67. Bernard L, Stern R, Lew D, Hoffmeyer P. Serotonin syndrome after concomitant treatment with linezolid and citalopram. Clin Infect Dis. 2003;36:1197.
68. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. Ann Intern Med. 1992;117:390–8.
69. Gorwitz RJ JD, Powers JH, Jernigan JA. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention. Washington, DC; 2006.
70. Proctor RA. Role of folate antagonists in the treatment of methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis. 2008;46:584–93.
71. Johnson MD, Decker CF. Antimicrobial agents in treatment of MRSA infections. Dis Mon. 2008;54:793–800.
72. Yourassowsky E, van der Linden MP, Lismont MJ, Crokaert F. Combination of minocycline and rifampicin against methicillin- and gentamicin-resistant *Staphylococcus aureus*. J Clin Pathol. 1981;34:559–63.
73. Atkins B, Gottlieb T. Fusidic acid in bone and joint infections. Int J Antimicrob Agents. 1999;12:79–93.
74. Drancourt M, Stein A, Argenson JN, et al. Oral treatment of *Staphylococcus* spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. J Antimicrob Chemother. 1997;39:235–40.
75. Turnidge J, Collignon P. Resistance to fusidic acid. Int J Antimicrob Agents. 1999;12:35–44.
76. Darley ES, MacGowan AP. Antibiotic treatment of gram-positive bone and joint infections. J Antimicrob Chemother. 2004;53:928–35.
77. Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. Clin Infect Dis. 2008;46:1069–77.
78. Lew DP, Waldvogel FA. Use of quinolones in osteomyelitis and infected orthopaedic prosthesis. Drugs. 1999;58:85–91.
79. •• Cordero-Ampuero J, Esteban J, Garcia-Cimbrelo E. Oral antibiotics are effective for highly resistant hip arthroplasty infections. Clin Orthop Relat Res. 2009;467:2335–42. *Feasibility of oral antibiotic regimens even for arthroplasty-related osteomyelitis*.
80. Greenberg RN, Newman MT, Shariaty S, Pectol RW. Ciprofloxacin, lomefloxacin, or levofloxacin as treatment for chronic osteomyelitis. Antimicrob Agents Chemother. 2000;44:164–6.
81. Nelson CL. The current status of material used for depot delivery of drugs. Clin Orthop Relat Res. 2004;427:72–8.
82. Kanellakopoulou K, Giamarellos-Bourboulis EJ. Carrier systems for the local delivery of antibiotics in bone infections. Drugs. 2000;59:1223–32.
83. Walenkamp GH, Kleijn LL, de Leeuw M. Osteomyelitis treated with gentamicin-PMMA beads: 100 patients followed for 1–12 years. Acta Orthop Scand. 1998;69:518–22.
84. Uçkay I, Assal M, Legout L, et al. Recurrent osteomyelitis caused by infection with different bacterial strains without obvious source of reinfection. J Clin Microbiol. 2006;44:1194–6.
85. Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. J Antimicrob Chemother. 2003;51:1261–8.
86. Panda M, Ntungila N, Kalunda M, Hinsenkamp M. Treatment of chronic osteomyelitis using the Papineau technique. Int Orthop. 1998;22:37–40.

87. Leone S, Borre S, Monforte A, et al. Consensus document on controversial issues in the diagnosis and treatment of prosthetic joint infections. Int J Infect Dis. 2010;14:67–77.
88. Simpson AH, Deakin M, Latham JM. Chronic osteomyelitis. The effect of the extent of surgical resection on infection-free survival. J Bone Joint Surg Br. 2001;83:403–7.
89. Siegel HJ, Patzakis MJ, Holtom PD, et al. Limb salvage for chronic tibial osteomyelitis: an outcomes study. J Trauma. 2000;48:484–9.
90. Seghrouchni K, van Delden C, Dominguez D, et al. Remission after treatment of osteoarticular infections due to *Pseudomonas aeruginosa* versus *Staphylococcus aureus*: a case-controlled study. Int Orthop. 2011;36:1065–71.
91. Bauer T, David T, Rimareix F, Lortat-Jacob A. Marjolin's ulcer in chronic osteomyelitis: seven cases and a review of the literature. Rev Chir Orthop Reparatrice Appar Mot. 2007;93:63–71.
92. • Berendt AR, Peters EJ, Bakker K, et al. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. Diabetes Metab Res Rev. 2008;24:145–61. *Everything you want to know about diabetic foot osteomyelitis*.
93. Valabhji J, Oliver N, Samarasinghe D, et al. Conservative management of diabetic forefoot ulceration complicated by underlying osteomyelitis: the benefits of magnetic resonance imaging. Diabet Med. 2009;26:1127–34.
94. Byren I, Peters EJ, Hoey C, et al. Pharmacotherapy of diabetic foot osteomyelitis. Expert Opin Pharmacother. 2009;10:3033–47.
95. Venkatesan P, Lawn S, Macfarlane RM, et al. Conservative management of osteomyelitis in the feet of diabetic patients. Diabet Med. 1997;14:487–90.
96. • Game FL, Jeffcoate WJ. Primarily non-surgical management of osteomyelitis of the foot in diabetes. Diabetologia. 2008;51:962–7. *Feasibility of conservative management of chronic diabetic toe osteomyelitis*.
97. Uçkay I, Vernaz-Hegi N, Harbarth S, et al. Activity and impact on antibiotic use and costs of a dedicated infectious diseases consultant on a septic orthopaedic unit. J Infect. 2009;58:205–12.