Antimicrobial treatment concepts for orthopaedic device-related infection

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Abstract

Successful management of orthopaedic device-related infections requires combined surgical and antimicrobial therapy. Because of the heterogeneity of clinical situations, controlled trials are lacking. Although rational concepts for surgical treatment have been published, many aspects of antimicrobial therapy are still not well documented. In this review, some of these knowledge gaps are discussed, and rational arguments for initial parenteral treatment are presented. In addition, the interpretation of data regarding bone penetration is discussed. Whereas rifampin is now a standard combination partner in the treatment of staphylococcal infections, its role against other microorganisms is still unclear. Finally, in view of the increasing prevalence of methicillin-resistant staphylococci and their decreasing susceptibility to vancomycin, data are provided on linezolid and daptomycin, which can potentially be used in bone and joint infections.

Keywords: Bone penetration, daptomycin, linezolid, orthopaedic device-related infection, rifampin, rifamycin derivatives

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Introduction

Orthopaedic implants are increasingly being used to relieve pain, allow rapid fracture healing, and improve both mobility and independence of patients. Although the overall percentage of complications after orthopaedic procedures is low, the absolute number is increasing, owing to the growing number of patients with implants. The treatment of orthopaedic device-related infection (ODRI) requires integrated and coordinated collaboration between orthopaedic surgeons and infectious diseases specialists. Rational treatment concepts have been proposed from expert groups [1–4]. In this review, we focus on antimicrobial therapy. Because few solid data for antimicrobial concepts have been published, this review is based on observational studies, pharmacological and experimental studies, and opinion statements.

Initial Antimicrobial Treatment

Rationale for initial intravenous therapy

After microbiological sampling, intravenous antibiotics are administered for several reasons. At initial clinical presentation, a high bacterial load is commonly found at the infection site. Hence, the risk for emergence of resistance is highest during this period, especially with subinhibitory antimicrobial concentrations. Enteral resorption may be compromised during the early postoperative period, whereas, with intravenous therapy, bioavailability is predictable. In addition, much higher doses of many compounds (e.g. β-lactams) can be administered intravenously than by the oral route. In our view, the latter argument is important, because the concentration–time course in the bone compartments is difficult to determine, in particular in the early phase of infection [5]. Hence, high serum antibiotic concentrations are required to
obtain antimicrobial levels above the expected bacterial MICs in the tissue compartment.

Factors influencing choice of compound
The case history, clinical findings and local epidemiology (e.g. methicillin-resistant staphylococci, in particular methicillin-resistant *Staphylococcus aureus*) allow an educated guess regarding the empirical choice of antimicrobial agent. Antimicrobial resistance may emerge during treatment against staphylococci, mainly when quinolones, rifampin or fusidic acid are used [6–8], or during treatment against *Pseudomonas aeruginosa* when quinolone is administered [9]. Therefore, these agents cannot be recommended during the initial treatment phase. In contrast, the emergence of β-lactam resistance does not occur during anti-staphylococcal therapy. The choice and doses of antimicrobial compound should be made after considering: (i) potential causative microorganisms and their corresponding range of MICs; (ii) pharmacodynamic and pharmacokinetic properties; (iii) mechanism of action (Table 1); (iv) tolerability; and (v) host toxicity [10–17].

Start and dosage of rifampin therapy
No study has investigated the optimal time for starting rifampin therapy in patients with staphylococcal ODRI. Concerns regarding liver toxicity or drug interactions with compounds used for anaesthesia have been raised when rifampin is administered preoperatively or immediately after surgery. In one controlled study, it was started immediately after surgery [6], and neither significant liver toxicity nor relevant drug interactions were observed. From a pharmacological point of view, this is plausible, because hepatitis is infrequently associated with rifampin, and enzyme induction may become clinically relevant after several days [18]. However, it is prudent not to use rifampin in the early course of infection, for the following reasons. First, perioperative rifampin therapy increases the risk of superinfection with rifampin-resistant staphylococci by selection pressure on the local flora [19]. Second, emergence of resistance is highest when the bacterial load is high [7]. Thus, there are arguments for not starting rifampin combination therapy before all drains are removed, the wound is dry, and the bacterial load is lowered by surgical treatment and initial antimicrobial therapy.

The optimal daily dosage and frequency of rifampin administration are unknown. Different regimens have been published, although they have not been compared with each other; they range from 300 mg twice daily [20] or 600 mg once daily [21] to 450 mg twice daily [6] or 900 mg once daily [22] (Table 2). The activity of rifampin is based on Cmax/MIC. Hence, extrapolating these regimens will probably reveal different Cmax/MIC values. Nevertheless, the clinical outcome data do not suggest that one regimen is clearly less effective than the other. In our experience, 900 mg once daily is often not well tolerated. Thus, side effects and compliance with co-administered drugs (e.g. quinolones twice daily) should influence the choice of regimen on an individual basis.

Switch from intravenous to oral drugs
Empirical therapy should be streamlined to directed intravenous therapy as soon as the susceptibility pattern of the microorganism(s) is known. Table 1 summarizes the most common antimicrobial drugs used for initial empirical and

### Table 1. Antimicrobial drugs used for initial intravenous empirical and directed therapy for orthopaedic device-related infection, and their serum concentrations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Efficacy</th>
<th>Dose</th>
<th>Cmax (mg/mL)</th>
<th>T1/2 (h)</th>
<th>C1h (mg/mL)</th>
<th>C2h (mg/mL)</th>
<th>C4h (mg/mL)</th>
<th>C8h (mg/mL)</th>
<th>Recommended daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin G</td>
<td>T &gt; MIC</td>
<td>5</td>
<td>130–235</td>
<td>0.5–0.67</td>
<td>50–80</td>
<td>2–3</td>
<td>1</td>
<td>≤0.1</td>
<td>24–25 Mio in 5–6 doses</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>T &gt; MIC</td>
<td>2</td>
<td>110</td>
<td>1.0–1.5</td>
<td>50</td>
<td>3.5</td>
<td>1.2</td>
<td>≤0.1</td>
<td>8 g in 4 doses</td>
</tr>
<tr>
<td>Clavulanate</td>
<td></td>
<td>0.2</td>
<td>14</td>
<td>1.0–1.5</td>
<td>8</td>
<td>0.7</td>
<td>0.2</td>
<td>≤0.1</td>
<td>0.8 g in 4 doses</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>T &gt; MIC</td>
<td>1</td>
<td>130–210</td>
<td>1.0–1.5</td>
<td>30–55</td>
<td>2–8</td>
<td>0.5–2</td>
<td>≤1</td>
<td>8 g in 4 doses</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>T &gt; MIC</td>
<td>1</td>
<td>188</td>
<td>1.5–2.0</td>
<td>74</td>
<td>16.5</td>
<td>6</td>
<td>2</td>
<td>8 g in 4 doses</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>T &gt; MIC</td>
<td>1</td>
<td>100</td>
<td>1.0–2.0</td>
<td>24</td>
<td>4</td>
<td>1.1</td>
<td>≤0.1</td>
<td>6 g in 4 doses</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>T &gt; MIC</td>
<td>1</td>
<td>200</td>
<td>8.0</td>
<td>190</td>
<td>75</td>
<td>55</td>
<td>–</td>
<td>2 g in 1 dose</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>T &gt; MIC</td>
<td>1</td>
<td>90</td>
<td>2.0–2.5</td>
<td>40</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>6 g in 3 doses</td>
</tr>
<tr>
<td>Cefepine</td>
<td>T &gt; MIC</td>
<td>2</td>
<td>163</td>
<td>2.0</td>
<td>86</td>
<td>19</td>
<td>4</td>
<td>–</td>
<td>6 g in 3 doses</td>
</tr>
<tr>
<td>Imipenem–cilastin</td>
<td>T &gt; MIC</td>
<td>0.5</td>
<td>45</td>
<td>1.0</td>
<td>21.5</td>
<td>2.6</td>
<td>0.6</td>
<td>–</td>
<td>2–4 g in 4 doses</td>
</tr>
<tr>
<td>Meropenem</td>
<td>T &gt; MIC</td>
<td>0.5</td>
<td>52</td>
<td>10</td>
<td>20</td>
<td>1–3</td>
<td>0.3–1.5</td>
<td>≤1</td>
<td>6 g in 3 doses</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>AUc0–24h</td>
<td>4.0</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 mg/kg in 2 doses</td>
</tr>
</tbody>
</table>

Cmax = maximum serum antibiotic concentration; C1h to C8h = serum antibiotic concentration after 1–8 h; T1/2 = half-life in serum; T > MIC = time for which the antibiotic concentration exceeds the microbial MIC; AUc0–24h/MIC = ratio of area under the concentration–time curve during a 24-h dosing period to MIC.

1Data from [10–16].

2After intravenous administration of the indicated dose, the illustrated plasma concentrations (Cmax and C1h, C2h, C4h) were measured.

3In the initial phase of treatment, the stated doses and intervals are based on the decrease in serum concentration (C1h to C8h) and the target to achieve high serum concentrations; they do not take into account the concentration–time course in the bone compartments. After measurement of MICs of the causative pathogen(s), the antibiotic concentration should preferably remain at ≥50% of the dosing interval above the MIC (T > MIC).

4Mio = 1 x 10^6 units of penicillin, corresponding to 0.6 g.

5Recommended doses are based on AUc0–24h/MIC and trough levels. For methicillin-resistant staphylococci, in particular methicillin-resistant *Staphylococcus aureus*, an AUc0–24h/MIC of >400 is recommended [17].

6The recommendations are for adult patients with normal liver and renal function.
TABLE 2. Oral antimicrobial compounds that are commonly used in osteomyelitis and have reasonable bone penetration

<table>
<thead>
<tr>
<th>Class</th>
<th>Compound</th>
<th>Recommended dose for ODRI [1,4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Levofloxacin</td>
<td>750 mg once daily or 500 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>750 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>400 mg once daily [26]</td>
</tr>
<tr>
<td>Lincosamide</td>
<td>Clindamycin</td>
<td>300–600 mg 4 times a day</td>
</tr>
<tr>
<td>Rifamycin</td>
<td>Rifampin</td>
<td>300–450 mg twice daily [6,20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or 600 mg once daily [21]</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Minocycline</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg twice daily</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>600 mg twice daily [28,32]</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Fusidic acid</td>
<td>500 mg three times a day</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulphasemethoxazole</td>
<td>1 DS three times a day</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>500 mg three times a day to four times a day</td>
</tr>
</tbody>
</table>

DS, double strength; ODRI, orthopaedic device-related infection.
<sup>a</sup>Data on bone penetration reviewed in [10,24,25].
<sup>b</sup>Clindamycin is bacteriostatic. Most data on bone penetration are from the 1970s. Limitations of the data should be considered (Table S1).
<sup>c</sup>Lack of data on bone penetration.
<sup>d</sup>Data only for the intravenous route [27]. The bioavailabilities with the intravenous route and the oral formulation are similar, indicating similar bone penetration.

Bone Penetration of Antimicrobial Agents

Several reviews have been published on the bone/serum ratio as a reflection of antibiotic concentration at the infection site [10,23–25]. The mean bone/serum concentrations for most antibiotics range between 0.1 and 0.3 [10,25]. These data are helpful when considering variables such as the MIC of the pathogen and the pharmacokinetic/pharmacodynamic parameters of a drug. They should, however, be interpreted with caution. Data are mainly obtained from uninfected bone samples harvested during joint replacement, and reflect bone/serum ratios after a single dose, not in an equilibrium state. Considering the long-term treatment commonly applied for ODRI s, it is important to note that bone/serum ratios change over time unless equilibrium between compartments has been reached (system hysteresis) [25]. Moreover, extracellular/serum and intracellular/s

Serum concentration ratios are often not distinguished [5]. Finally, the measurements can be made by using a variety of methods, which may also involve technical drawbacks, including the lack of validation guidance for stability, variability and linearity of the calibration curve, and the use of appropriate internal calibration standards (reviewed in [25]). In addition, methodological differences in sample preparation, homogenization of the bone and extraction of the antimicrobial compound may reveal results that are difficult to interpret for clinical practice. Moreover, bone/serum ratio data frequently do not provide information on whether or not the antibiotic is active [5]. The considerations that should be taken into account when published bone/serum concentration ratios are used are presented in Table S1 [5,25].

In the treatment of ODRI, differentiating between chronic infection with an established biofilm and acute postoperative or haematogenous infection is important. Bone sequestrations are often present in chronic but not in acute ODRI. Thus, in chronic ODRI, antibiotic bone penetration and activity against biofilm bacteria is important.

Despite these limitations of the available bone/serum concentration data, good bone penetration has been shown for several oral antibiotics. For example, fluoroquinolones and linezolid have bone/serum ratios ranging from 0.3 to 1.2 and from 0.2 to 0.5, respectively [10,24,25]. Table 2 summarizes the oral antimicrobial compounds that are commonly used in osteomyelitis and have reasonable bone penetration. Most data, however, arise from monotherapy [10,24–27], whereas combination therapy is common for the treatment of ODRI [28–32]. Thus, the respective role of each component in the combination regimen against ODRI is clinically undefined, except for quinolone–rifampin combinations [6].

Rifampin for Treatment of Pathogens other than Staphylococci

The rationale and benefit of combination therapy with rifampin for staphylococci has been shown in various studies [6,33,34]. The role of rifampin in ODRI s caused by other Gram-positive bacteria is still unclear.

Streptococcus species

The evidence on rifampin combination therapy is poor. Rifampin is, however, commonly very active against most streptococci, including nutritionally variant species [35–40]. Nevertheless, its effect on streptococcal biofilms is not proven [41]. Penicillin is still the treatment of choice against streptococci. In vitro, the combination of penicillin and
rifampin does not seem to be superior to penicillin alone. With the checkerboard MIC technique, Maduri-Traczewski et al. [42] detected synergism in 52% and no antagonism in 88 strains of group B streptococci. However, when minimal bactericidal concentrations were considered, antagonism was noted in 70% of the same strains. With respect to clinical data, the use of rifampin combination therapy was reported in a few case reports/series involving prosthetic valve endocarditis caused by nutritionally variant streptococci [43,44], and periprosthetic joint infections (PJIs) caused by β-haemolytic streptococci [45]. The effect of adding rifampin remains unclear, however, when the outcome is not compared with that of control patients. Taken together, these findings show that, although rifampin is highly active against many streptococci in vitro, there is no evidence for its use, neither alone nor in combination, in patients with ODRI.

**Enterococcus species**

Rifampin is active against enterococci in vitro, but it is only bacteriostatic against most strains. However, resistance emerges rapidly [46]. In animal and in vitro models, rifampin combined with other agents (e.g. penicillin, ampicillin, vancomycin, and gentamicin) did not provide a significant advantage over the combination drug alone [46,47]. Ampicillin and rifampin were even reported to be antagonistic [48]. The published experience with rifampin for the treatment of enterococcal infection in humans is scarce [49]. Recently, Holmberg et al. [50] evaluated the activity of ciprofloxacin, ampicillin, vancomycin, and linezolid, alone and in combination with rifampin, against biofilms caused by Enterococcus faecalis isolates obtained from PJIs. Similar to the results of previous in vitro studies, the addition of rifampin to ampicillin or vancomycin was not beneficial. However, the combination of linezolid and rifampin, and that of ciprofloxacin and rifampin, was more efficient in reducing the biofilm than each compound alone [50]. In addition, the emergence of rifampin resistance was less frequent in combination therapy than in monotherapy. Although this in vitro study gives a new option for enterococcal treatment, clinical data are lacking.

With the introduction of tigecycline, rifampin–tigecycline combination therapy for ODRI has been considered. A recent in vitro and animal study with clinical enterococcal isolates from surgical wound infections showed synergism in the combination as compared with tigecycline alone [51]. However, these results cannot be extrapolated to ODRI in clinical practice. In summary, Enterococcus species remain difficult-to-treat pathogens that often persist or cause relapsing infections [52]. Combination therapy with rifampin plus linezolid, daptomycin or tigecycline needs further investigation. At this stage, the use of rifampin in enterococcal ODRI cannot be recommended.

**Propionibacterium species**

These pathogens are generally susceptible to rifampin. Although there are no EUCAST MIC breakpoints, it seems reasonable to use a breakpoint of $R > 0.5$ mg/L [53]. Considering this value, the emergence of resistance seems possible (patient 8 in [54]). Hence, and despite the results from an animal study showing a considerable cure rate with rifampin monotherapy [55], the compound should not be administered alone. In an ODRI animal study, the combination of daptomycin and rifampin achieved a cure rate of 63% [55]. Experimental or clinical data on penicillin–rifampin, or on clindamycin–rifampin, are lacking. Although rifampin combinations have been used with clindamycin, amoxyccillin, and daptomycin [56–61], the benefit of adding rifampin remains unknown without a study comparing the combination with monotherapy.

In the case of two-stage exchange of foreign material, there is no rationale for the use of rifampin, as Propionibacterium is highly susceptible to antibiotics, and commonly loses its pathogenicity as soon as the device is removed. For other surgical procedures (e.g. debridement and implant retention), clinical data are lacking, although animal data are promising.

**Gram-negative bacteria (GNB)**

These bacteria are able to form biofilms, and they are playing an increasing role in ODRI [62–65]. Rifampin is a hydrophobic compound that does not pass well through the membranes of GNB. However, in combination with antibiotics that permeabilize the bacterial membrane (e.g. colistin), rifampin is effective against GNB [66–68]. Moreover, for *P. aeruginosa* and *Acinetobacter baumannii*, in vitro and animal studies have demonstrated synergistic activity when rifampin and colistin are used (reviewed in [69,70]). Few studies have investigated the susceptibility of biofilm-grown *Burkholderia cepacia* and *P. aeruginosa* (isolates obtained from patients with cystic fibrosis) to antibiotic combinations [71]. However, these data cannot be simply extrapolated to biofilm bacteria that adhere to foreign bodies. In summary, the published data on colistin–rifampin are not sufficient to recommend this concept for ODRI.

**Other Rifamycin Derivatives**

Rifampin is a strong inducer of cytochrome P450 (CYP) isoenzyme CYP3A4 and, to a lesser extent, CYP2C8 and CYP2C9, which increase the metabolism of many other co-
administered drugs, thereby decreasing their serum concentrations [18]. To maintain the serum level of the co-administered drug, its dose must be increased, and this may compromise the patient’s compliance. As the presence of comorbidities and therefore comedication is the rule in patients with ODRI, rifamycin derivatives with less potential for interaction are needed. The grading of CYP induction caused by rifamycins is as follows: rifampin > rifapentine > rifabutin > ABI-0043.

### Rifapentine

This rifamycin derivative has an increased half-life as compared with rifampin, and is active against *Mycobacterium tuberculosis*. Activity against staphylococci has also been shown *in vitro*, revealing similar results to those for rifampin [72, 73]. There are no data on the use of rifapentine in foreign-body infections. Rifapentine is administered once weekly for (latent) tuberculosis, making the compound attractive for compliance, but difficult for management of drug interactions. Therefore, without data from clinical studies, it is not a feasible alternative to rifampin for ODRI.

### Rifabutin

Most data on drug interactions with rifabutin relate to antiretroviral medications in human immunodeficiency virus patients treated for tuberculosis. Rifabutin has bactericidal effects on staphylococci, and also acts intracellularly [74]. To our knowledge, no published data exist on the use of rifabutin combination therapy in ODRI. However, in selected cases, namely solid organ transplant (e.g. treatment with everolimus) or human immunodeficiency virus patients (e.g. treatment with protease inhibitors), the use of rifabutin (300 or 450 mg once daily) seems reasonable (unpublished observations). Importantly, the trough level of the co-administered drug must be closely monitored, both during treatment and after its cessation. Notably, protease inhibitors inhibit CYP enzymes and cause an increase in serum rifabutin levels. Hence, potential toxic side effects of rifabutin must also be monitored.

**ABI-0043**

This rifamycin derivative has no CYP drug–drug interactions, no strict cross-resistance with other rifamycins, and very low MICs for staphylococci and streptococci [75]. Moreover, in an experimental model of foreign-body infection, it showed excellent activity against staphylococci. In combination with levofloxacin, ABI-0043 cleared *S. aureus* from the cage fluid and cured foreign-body infection in 92% (22/24) of experiments [76]. However, clinical studies are still lacking.

### Antimicrobial Treatment for ODRI caused by GNB

In ODRI caused by GNB, like that caused by staphylococci [6], the duration of symptoms (i.e. acute) and the condition of the soft tissue is crucial for the outcome if debridement and implant retention are performed [62, 64, 65, 77]. Resistance to quinolones in GNB is associated with treatment failure, requiring implant removal [65]. However, in patients fulfilling the criteria for debridement and implant retention, intravenous therapy with cephalosporins or carbapenems (Table 1), followed by oral quinolones, is recommended. In contrast, both clinical observation and experimental results from a foreign-body animal model showed treatment failure with co-trimoxazole for ODRI [78]. However, co-trimoxazole may be a valuable alternative for treating the adjacent bone infection after device removal.

The most important factors in choosing an antimicrobial compound for intravenous empirical and directed therapy are the local epidemiology (e.g. prevalence of extended-spectrum β-lactamase producers), species identification and their potential properties (e.g. AmpC producers), and the results from correct antimicrobial susceptibility testing.

### Linezolid and Daptomycin

The most frequent microorganisms causing PJIs are staphylococci [1]. The prevalence of methicillin-resistant staphylococci is increasing, and their susceptibility to vancomycin is decreasing [79]. Therefore, the relevance of novel anti-staphylococcal drugs, such as linezolid and daptomycin, for the treatment of ODRI should be reviewed [80]. Notably, neither antibiotic is approved for bone and joint infections.

### Linezolid

This compound is the first substance of a new class of antimicrobial agents, the oxazolidinones. With current resistance patterns, the steady-state peak plasma concentration of linezolid significantly surpasses the MIC90 of enterococci and staphylococci [81]. It also has good penetration in human bone [25]. Nevertheless, its use in bone and joint infections is not promising [82]. In a rat model of *S. aureus* osteomyelitis, the cure rate was disappointing [83]. When it is used in combination with rifampicin, however, the eradication of biofilm infections is better [84]; in a model of subcutaneous implant-associated infection, 50% of methicillin-resistant *S. aureus* infections could be cured with the combination therapy [85]. Despite several observational studies in humans
linezolid efficacy in ODRI cannot be unambiguously judged. The populations in these studies were heterogeneous, and no clear protocols for the definition of cure were used. However, Soriano et al. [32] analysed 85 patients with ODRI (24 acute and 61 chronic infections). In patients with implant removal, the cure rates were similar with linezolid alone and with linezolid combined with rifampin (92% (22/24) vs. 100% (8/8)). In contrast, in patients with implant retention, monotherapy had a lower cure rate than combination therapy (47% (14/30) vs. 61% (14/23)). Notably, the best cure rate with implant retention was observed in patients with acute infections and combination therapy (87.5% (7/8)). Although the latter constellation is a treatment option, the side effects of linezolid must be considered. Because bone and joint infections generally require prolonged treatment, the use of linezolid remains controversial.

Daptomycin
This compound is a cyclic lipopeptide antibiotic with concentration-dependent bactericidal activity against Gram-positive microorganisms [90]. The bactericidal effect occurs irrespective of inocula and bacterial growth phase [91–93]. Previous clinical trials were interrupted because of muscle toxicity. This was observed when daptomycin was administered twice daily [94]. With once-daily application, this side effect did not differ from comparators. Even at high doses (8 mg/kg), and with prolonged treatment (up to 82 days), it was generally well tolerated, and rarely (<5%) caused musculoskeletal symptoms [95].

In ODRI, daptomycin monotherapy appears not to be a good option, because adherent staphylococci are phenotypically resistant to daptomycin. Indeed, monotherapy showed a low cure rate in animal models of implant-associated infections [94,96]. In addition, in 12 patients with PJI caused by staphylococci, daptomycin (monotherapy, 4 mg/kg for a minimum of 6 weeks) showed a low success rate [97]. However, at higher doses (6–10 mg/kg), daptomycin might be a relevant combination partner for rifampin for the treatment of ODRI. The combination was highly efficacious in animal models of implant-associated infections [92,96,98]. Moreover, in these experiments, combination therapy could completely prevent the emergence of rifampin resistance [92]. Nevertheless, the efficacy of daptomycin for ODRI cannot be conclusively judged, because there are few clinical data. Analysis of the Cubist database is not helpful. Of 124 evaluable daptomycin-treated patients with osteomyelitis, post-treatment results of patients with an ODRI were available for only 17 [99]. Notably, only three were treated with retention. Nevertheless, these data allowed at least dose finding, because patients with a dose of >4 mg/kg had a better outcome than those with a lower dose (29% vs. 4% failure, p 0.013) [99].

In summary, the current clinical data do not allow the recommendation of daptomycin routinely for ODRI. However, if daptomycin is considered for selected cases, the available data point towards treatment: (i) with doses of 6–10 mg/kg once daily; and (ii) in combination with rifampin. During prolonged treatment, creatine phosphokinase surveillance is needed to rapidly detect muscle toxicity.

Transparency Declaration

W. Zimmerli received a travel grant and Advisory Board fees from Pfizer, Inc.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Technical considerations regarding published bone/serum concentration ratios.

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