Oral antibiotic treatment of staphylococcal bone and joint infections in adults

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Bone and joint infections, especially implant-associated infections, are difficult to cure. Long-term antibiotic therapy, combined with appropriate surgery and the removal of prostheses, is required. The most common causative organisms in bone and joint infections are staphylococci. Oral agents are often used after an initial course of parenteral antibiotic treatment. However, it is unclear which oral regimens are most effective in staphylococcal bone and joint infections. We review various oral antibiotic regimens and discuss which regimens are effective for this indication.

Keywords: antimicrobial treatment, Staphylococcus, osteomyelitis, infectious arthritis, orthopaedic fixation devices, joint prosthesis

Introduction

Bone and joint infections, especially implant-associated infections, are difficult to treat. The most common organisms causing bone and joint infections are staphylococci, including Staphylococcus aureus and coagulase-negative staphylococci.1–4 To cure these infections, long-term antibiotic treatment combined with appropriate surgery and removal of the implant is necessary.

Despite the paucity of large prospective randomized clinical trials evaluating the efficacy and safety of oral therapy, and the heterogeneity of bone and joint infections, recent systematic reviews show that oral therapy is as effective as parenteral therapy provided that the agents used.5–7 Oral antibiotic agents, alone or combined, are used for long-term treatment after the initial therapy with parenteral agents.8 Previous reviews on the treatment of bone and joint infection have recommended certain oral agents for long-term therapy, although limited data on these antibiotic regimens have been reported.9–11 The most recent clinical practice guidelines published by the Infectious Diseases Society of America recommend a combination of rifampicin and fluoroquinolone as a first-line regimen when an agent active against biofilms is needed, and include several other antibiotics for the oral therapy of prosthetic joint infection (PJI).12 However, the background of these recommendations on what oral antibiotics should be used has not been clearly indicated, except for the combination of rifampicin and fluoroquinolone. We summarize here the available evidence on the choice of oral antibiotics for staphylococcal bone and joint infection. To determine effective oral antibiotic regimens, we reviewed the literature on pharmacokinetic characteristics, animal models and clinical studies of oral agents against staphylococcal bone and joint infections.

Search strategy and selection criteria

We searched Medline for articles published in English. No other restrictions were applied. The last search was done on 10 May 2012. The search algorithm was 'staphylococcus AND (osteomyelitis OR arthritis OR [(bone OR joint OR orthopedic OR implant) AND infection]) AND names or classes of antibiotics used in the treatment of staphylococcal infections'. By searching the reference lists of the retrieved articles, we also identified relevant articles published in other languages and included them if appropriate. Each article was assessed for its clinical relevance and the quality of its methodology. Preference was given to randomized comparative trials focusing on oral antibiotic treatment regimens for staphylococcal bone and joint infections. However, the majority of the articles were case reports or observational studies, and only a few were randomized clinical trials. Therefore, although relevant clinical trials or animal studies were preferred, this review is mainly based on experimental models, historical observational studies, non-randomized clinical trials and the guidelines of expert societies.

Commencing oral antibiotic therapy

In the management of bone and joint infections, the selection of antibiotic regimens and the duration of antibiotic therapy vary depending on the clinical setting and the treatment approaches available.9 Usually, an initial short course of intravenous treatment is given to reduce the bacterial burden and thereby minimize the risk of emergence of resistance to oral agents.15 Intravenous therapy is administered for the first 2–4 weeks, followed by long-term oral therapy to complete the treatment.9 Recent evidence indicates that an early switch to oral therapy is effective in patients...
with PJIs. In that publication, intravenous therapy for 10–14 days was followed by a switch to oral antibiotics either for 6–8 weeks or for up to 3 months, depending on the type of infection and the clinical conditions. An even shorter course of parenteral therapy of less than 7 days before oral switching was recently used for children with acute haematogenous osteomyelitis. The limited evidence relating to the treatment of chronic osteomyelitis in adults suggests that the method of antibiotic administration (oral versus parenteral) does not affect the rate of disease remission provided the bacteria are susceptible to the antibiotic used. Although oral antibiotic therapy is increasingly being shown to have promise for treating chronic osteomyelitis in adults, more evidence from comparative trials with adequate statistical power is necessary.

Duration of oral antibiotic therapy

The optimum duration of antibiotic treatment for bone and joint infections remains unknown because this has never been studied in prospective randomized studies. For osteomyelitis, a total duration of 4–6 weeks of antibiotic therapy (after the last major debridement surgery) is generally recommended. The suggested duration of oral antibiotic therapy in patients with implant retention or a one-stage exchange, based on a controlled trial in patients with orthopaedic implant-associated infection, is 3 months for hip prostheses and 6 months for knee prostheses. In patients with fracture fixation devices, it is recommended that the duration of oral antibiotic therapy be 3 months when the device is retained and 6 weeks when all devices have been removed. Long-term oral suppressive antibiotics may be considered in selected cases, particularly if it is not possible to remove the device. For vertebral osteomyelitis, the recommended total duration ranges from 4–6 weeks to 3 months. Prolonged antibiotic treatment is recommended in patients with undrained abscesses or spinal implants. For arthritis, a 2–3 week course of therapy is suggested.

Selection of oral antibiotic agent

Several factors should be considered when selecting oral antibiotics to treat bone and joint infections. These include the type of infection, the extent of debridement when applicable, the antibiotic susceptibility of the pathogen, antibiotic penetration into the bone and joint tissues, oral bioavailability and cost. The drug(s) selected must have activity against the isolated organism and have a low risk for the development of adverse reactions and drug–drug interactions.

The presence of a foreign body may also be one of the most important factors in choosing the antibiotic regimen. In the presence of a foreign body, there are slow-growing or adherent organisms in biofilms, against which antibiotic efficacy is diminished. Therefore, for managing staphylococcal bone and joint infections, especially implant-associated infections, an optimal antibiotic agent should have activity against surface-adherent, slow-growing and biofilm-associated pathogens. It is notable that standard antibiotic susceptibility tests, which evaluate drug efficacy on freely growing bacteria in the logarithmic growth phase, are not reliable in predicting the outcome of implant-associated bone and joint infections. Their only use is to exclude antibiotic agents without in vitro efficacy.

Antibiotic bone penetration is also an important factor to consider, especially in the treatment of orthopaedic implant-associated infection, because it often has bone sequesters and an established biofilm. Regarding data on bone penetration, readers are advised to refer to an excellent review by Landersdorfer et al.

Monotherapy versus combination therapy

Whether monotherapy or combination therapy is more effective in staphylococcal bone and joint infections, especially implant-associated infections, remains unanswered. In a retrospective cohort study of implant-associated infections caused by methicillin-resistant S. aureus (MRSA) (44% with prosthetic joints and 56% with osteosynthesis devices), 35% of the patients experienced treatment failure, and monotherapy (hazard ratio 4.4, 95% CI 1.2–16.3; P=0.025) was an independent predictor of treatment failure. Most of the combination therapy regimens contained rifampicin. These findings suggest that combination therapy with rifampicin should be considered for patients with MRSA implant-associated infection, especially when implant removal is not feasible. It should be noted that the primary aim of antibiotic combination therapy is to decrease the risk of emergence of resistance to a companion drug or to provide synergistic or additive antibacterial activity.

Monotherapy

Rifampicin

Rifampicin has excellent oral bioavailability (70%–90%) and potent antistaphylococcal activity. It is also able to penetrate biofilms and has good activity in them. It can eradicate adherent and stationary-phase staphylococci with MICs 10–100 times higher than those for proliferative-phase organisms. The efficacy of rifampicin in staphylococcal bone and joint infections has been proven in many animal models (Table 1). As a single agent, it is more active than fusidic acid or ciprofloxacin against MRSA retrieved from device-associated biofilm infections. Therefore, it is a critically important antibiotic in the treatment of bone and joint infections, especially where implants are retained.

Resistance to rifampicin develops readily as a result of single point mutations in the DNA-dependent RNA polymerase gene. Rifampicin-resistant mutants were recovered at a frequency of around 10–9 in rifampicin monotherapy, whereas they were not recovered (frequency <10–11) in combination therapy with rifampicin/fusidic acid. Therefore, an adequate companion drug must be used to prevent the emergence of rifampicin resistance. Nevertheless, rifampicin resistance may still emerge when the inoculum of bacteria is high or surgical drainage is inadequate.

Fluoroquinolones

Fluoroquinolones are active against staphylococci in vitro, but are less active, compared with rifampicin, against adherent staphylococci, which these agents can rarely eradicate when given alone. They exhibit high bone to serum concentrations, and bone concentrations are higher than the MIC90 for the causative organisms. Newer fluoroquinolones (such as levofloxacin, moxifloxacin, gatifloxacin and gemifloxacin) tend to have lower MICs for Gram-positive pathogens than do older fluoroquinolones (such as ciprofloxacin and ofloxacin) and have a higher barrier to the emergence of resistance. Older fluoroquinolones when used alone in staphylococcal infections tend to select resistant mutants. To prevent the emergence of resistance, older fluoroquinolones are recommended in combination with other agents.
In the case of newer fluoroquinolones, monotherapy has been proven to be effective in decreasing bacterial counts in the bone and joint fluid and in biofilms in animals with implant-associated staphylococcal infections. Fluoroquinolone-resistant mutants did not emerge during monotherapy with levofloxacin or moxifloxacin in animal models. Newer fluoroquinolones such as moxifloxacin are at least as active against staphylococci as β-lactam and glycopeptide antibiotics in animal models of arthritis and chronic implant-associated osteomyelitis.

Fluoroquinolones have been used as single agents against chronic osteomyelitis caused by staphylococci (Table 2). In a recent study of orthopaedic implant-associated staphylococcal infections, the overall cure rate with moxifloxacin monotherapy (400 mg/day for 3 months) was 82.6%, and the cure rate for patients retaining implants was 71.4%. In that study, 77% of the patients underwent surgery and the implant was retained in 43.8%. Of the eight patients who relapsed, six had microbiologically confirmed disease, and all the organisms recovered were susceptible to fluoroquinolone. The investigators in that study suggested that fluoroquinolone monotherapy might be a suitable option for the long-term treatment of bone and joint infections caused by fluoroquinolone-resistant staphylococci. However, as fluoroquinolone monotherapy may induce resistance, we think that this approach should be employed only when alternative regimens are not available.

**Fusidic acid**

Fusidic acid is a bacterial protein synthesis inhibitor with antibiotic activity against staphylococci, including methicillin-resistant organisms. It has good penetration into infected bone and joints, and although it is less effective than rifampicin, it has activity against staphylococcal biofilms. Fusidic acid-resistant strains occur naturally at a rate of between $10^{2.6}$ and $10^{2.8}$ cfu. The rate of emergence of resistance reached 5.1% with fusidic acid monotherapy while it was less than 1% with fusidic acid combination therapy. Fusidic acid monotherapy is not a rational option for staphylococcal bone and joint infections, although there are old reports describing experience with it. The use of fusidic acid is generally restricted to oral maintenance treatment in combination with other agents such as rifampicin or a fluoroquinolone. Fusidic acid, combined with other agents, has been used for more than 40 years for various staphylococcal bone and joint infections, including acute and chronic osteomyelitis, arthritis and other orthopaedic infections.

**Linezolid**

Linezolid has antibiotic activity against a wide spectrum of Gram-positive organisms. It does not cause cross-resistance to antibiotic agents of other classes, and it does not require its dose to be adjusted according to renal and hepatic function. The concentration of linezolid in bone and joint fluid is high enough to treat infections. When 600 mg of linezolid was given orally every 12 h over 48 h, its mean concentration in cancellous bone 90 min after the final dose was at least twice the MIC$_{90}$ (4 mg/L) for staphylococci.
In one animal study, it was not effective for the treatment of chronic S. aureus osteomyelitis.43 Thrombocytopenia and anaemia may occur due to duration-dependent reversible myelosuppression, especially in patients receiving linezolid for more than 2 weeks.71 Irreversible peripheral neuropathy may also occur with prolonged treatment.72 Such adverse reactions, along with its high cost, are major obstacles to the wide use of this potent drug in staphylococcal bone and joint infections. Linezolid has been used for a variety of bone and joint infections in humans (Table 3). Even though the conditions varied between trials, clinical cure rates were 55%–100%.73 – 77

Trimethoprim/sulfamethoxazole

Trimethoprim/sulfamethoxazole has been used to treat staphylococcal bone and joint infections in children,78 as well as in adults.79 Rates of trimethoprim/sulfamethoxazole resistance among S. aureus isolates are highly variable and increasing.80 Time–kill studies indicate that trimethoprim/sulfamethoxazole is rapidly bactericidal against MRSA at concentrations four times the MIC.81 Trimethoprim penetrates bone at about 50% of serum levels, while sulfamethoxazole penetration is somewhat lower (15%).82 Concentrations of trimethoprim in synovial fluid approach serum levels, whereas sulfamethoxazole does not as readily penetrate into the synovial fluid.83 Oral trimethoprim/sulfamethoxazole alone has been used to treat staphylococcal bone and joint infections.84 In a recent study, oral trimethoprim/sulfamethoxazole at high doses was used as an alternative to conventional parenteral therapy in patients with staphylococcal orthopaedic implant-associated infections.85 However, trimethoprim/sulfamethoxazole treatment is not suitable for infections with abscesses or a lot of necrotic tissue because the availability of exogenous thymidine may bypass the double biosynthetic blockade of trimethoprim/sulfamethoxazole.86 In summary, trimethoprim/sulfamethoxazole as a monotherapy can be a therapeutic option for patients with staphylococcal bone and joint infections, particularly to complete an extended course of therapy after the bacterial burden has been reduced.84

Lincosamides

Clindamycin has been used either alone or in combination for the long-term oral therapy of staphylococcal bone and joint infections. It has excellent bone penetration and oral bioavailability. However, a recent literature review shows that it has only the same or a slightly higher bone penetration than β-lactams.84 It is not generally recommended if the target organism is erythromycin resistant, because a single-step resistance mutation due to the MLSβ mechanism can occur.87 Staphylococcal isolates that are clindamycin susceptible, but erythromycin resistant, should be tested for inducible clindamycin resistance using the D-test.87 D-test-positive organisms are likely to develop resistance to clindamycin during treatment.88

Clindamycin has been successfully used against staphylococcal bone and joint infections, especially in children,89,90 but rarely in adults.91 The use of clindamycin in MRSA osteomyelitis is suggested for two situations: extended courses of oral clindamycin, which may be used in patients who display osteomyelitis that is refractory to other agents, and community-acquired MRSA
infections, which often retain susceptibility to clindamycin. A recent guideline suggests that clindamycin can be considered for the treatment of bone and joint infections caused by susceptible staphylococci where inducible MLS B resistance has been excluded.93

Streptogramins

Pristinamycin is an oral streptogramin antibiotic consisting of two structurally unrelated, but synergistic, compounds, pristinamycin IA and pristinamycin IIA. It has been available in Europe for over 30 years for treating respiratory tract, skin and soft-tissue infections caused by susceptible Gram-positive bacteria. Pristinamycin is mainly active against Gram-positive bacteria including erythromycin-resistant staphylococci and MRSA. Recent clinical studies have also demonstrated the usefulness of pristinamycin for bone and joint infections. In one study, oral pristinamycin achieved cure or suppression in 21 of 22 patients with staphylococcal bone and joint infections.96 It appears to be a well-tolerated, effective oral alternative agent for treating difficult-to-treat bone and joint infections caused by staphylococci, particularly where there is intolerance of or resistance to rifampicin or fusidic acid.95,96

Tetracyclines

Tetracyclines are not as widely used for treating staphylococcal infections as they once were. Long-acting tetracyclines such as doxycycline and minocycline have good oral bioavailability and tissue penetration, and better antistaphylococcal activity than tetracycline. The antistaphylococcal activity of minocycline is better than that of doxycycline in vitro, but clinical superiority has not been demonstrated. Clinical data on the use of tetracyclines, singly or in combination, against staphylococcal bone and joint infections are very sparse. A recent review does not support their use as monotherapy in cases of osteomyelitis because of the present insufficiency of clinical data. The antibiotic-resistant activity of minocycline has been achieved in staphylococcal bone and joint infections caused by staphylococcal infections, which often retain susceptibility to tetracyclines.92 Recent clinical studies have also demonstrated the usefulness of pristinamycin for bone and joint infections caused by susceptible staphylococci, where inducible MLS B resistance has been excluded.93

Macrolides

Erythromycin has low bone penetration. It has poor penetration into biofilms produced by MRSA. In contrast, azithromycin has a long half-life in serum and tissues, and its bone concentrations are higher than its serum concentrations. However, azithromycin was ineffective in experimental staphylococcal osteomyelitis despite concentrations in bone that markedly exceeded the MIC. Macrolides should not be used as monotherapy in staphylococcal bone and joint infections.101

Fosfomycin

Fosfomycin has excellent in vivo activity against many Gram-positive and Gram-negative organisms, including methicillin-resistant and coagulase-negative staphylococci. Only low rates of adverse events, mainly mild gastrointestinal distress, have been reported. It has been shown to achieve levels in bone tissue well above the expected MICs for staphylococcal bone and joint infections, which often retain susceptibility to tetracyclines.92 Recent clinical studies have also demonstrated the usefulness of pristinamycin for bone and joint infections caused by susceptible staphylococci, where inducible MLS B resistance has been excluded.93

### Table 3. Summary of clinical studies of linezolid monotherapy for staphylococcal bone and joint infections

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Type of infection</th>
<th>Organism (n)</th>
<th>Overall clinical cure rate</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broder et al.</td>
<td>73</td>
<td>40 osteomyelitis, skin and soft-tissue infections</td>
<td>MSSA 3, MRSA 19, VRE 18</td>
<td>90.0% for osteomyelitis</td>
<td>—</td>
</tr>
<tr>
<td>Bassetti et al.</td>
<td>74</td>
<td>20 PJI</td>
<td>MRSA 14, MRCoNS 5, enterococci 1</td>
<td>80%</td>
<td>—</td>
</tr>
<tr>
<td>Aneziokoro et al.</td>
<td>75</td>
<td>20 osteomyelitis</td>
<td>MRSA 8, MSSA 1, CoNS 5, enterococci 3, streptococci 1, others 2, culture negative or not done 3</td>
<td>55%</td>
<td>—</td>
</tr>
<tr>
<td>Rao and Hamilton</td>
<td>76</td>
<td>53 PJI, osteomyelitis 25, others 5</td>
<td>MRSA 21, MSSA 6, MRCoNS 17,MSCoNS 2, enterococci 7</td>
<td>98.0% (49/50) in remission</td>
<td>16 treated with initial linezolid followed by long-term suppression with/without linezolid</td>
</tr>
<tr>
<td>Vercillo et al.</td>
<td>77</td>
<td>22 (14 evaluable) implant-associated osteomyelitis (18 with fracture fixation implants, 4 with arthroplasty implants)</td>
<td>monomicrobial 9 + polymicrobial 13, including MRSA 10 and VRE 5</td>
<td>100%</td>
<td>—</td>
</tr>
</tbody>
</table>

CoNS, coagulase-negative staphylococci; MRCoNS, methicillin-resistant coagulase-negative staphylococci; MSCoNS, methicillin-susceptible coagulase-negative staphylococci; MSSA, methicillin-susceptible S. aureus; VRE, vancomycin-resistant enterococci.

*aOnly studies for which the post-treatment follow-up period was more than 1 year are shown.*
common pathogens in diabetic patients with foot infections.\textsuperscript{103} However, in an animal model of MRSA osteomyelitis, 22.2\% (2/9) of rats were positive for MRSA in bone after 4 weeks of fosfomycin treatment.\textsuperscript{104} Studies of oral fosfomycin are very rare. This drug is a promising option, but the clinical efficacy of oral fosfomycin, alone or in combination with other antibiotics, should be adequately evaluated for the treatment of bone and joint infections.

\textbf{\textit{\textbeta}}-\textbf{Lactam antibiotics}

\textbf{\textit{\textbeta}}-Lactams, which inhibit cell wall synthesis, are inactive against biofilm-associated staphylococci, but are active when combined with rifampicin.\textsuperscript{105} Cefalotin combined with rifampicin was more effective than a rifampicin/tetracycline combination in young biofilms of \textit{Staphylococcus epidermidis} and at high concentrations, whereas the opposite was the case at lower concentrations in aged biofilms.\textsuperscript{106} Because of their limited bioavailability, oral dosing with \textbf{\textit{\textbeta}}-lactams is unlikely to achieve adequate bone levels.\textsuperscript{107} In one study, however, oral cefadroxil achieved adequate antibiotic concentrations in uninfected bone.\textsuperscript{108} Oral amoxicillin/clavulanate and some first-generation cephalosporins fulfilled the pharmacokinetic/pharmacodynamic requirements for clinical efficacy, especially in children.\textsuperscript{108} Amoxicillin/clavulanate was as effective as fluclaxacillin and clindamycin by subcutaneous injection in an experimental rat model of staphylococcal osteomyelitis.\textsuperscript{109}

Oral antibiotic therapy with \textbf{\textit{\textbeta}}-lactams has been successful against childhood bone and joint infections,\textsuperscript{110–112} which are usually haematogenous in origin and heal more rapidly than adult bone and joint infections. In one retrospective study involving 29 children with acute osteomyelitis treated with short-course parenteral antibiotics followed by oral cefalexin, none suffered treatment failure or complications at a 6 month follow-up.\textsuperscript{113} In a recent prospective study comparing oral first-generation cephalosporins (cefadroxin, cefalexin and cefadroxil) with oral clindamycin after intravenous antibiotics available so far, the rifampicin/fluoroquinolone combination has been the most frequently used against bone and joint infections (Table 4).\textsuperscript{115,123–133}

(1) \textbf{Rifampicin/fluoroquinolone combinations}

Although combinations of rifampicin and a fluoroquinolone yielded a variety of results against staphylococci \textit{in vitro}, these results may not correlate with outcomes in animal models or clinical infections.\textsuperscript{134} The rifampicin/fluoroquinolone combination seemed more effective than rifampicin alone in experimental MRSA osteomyelitis,\textsuperscript{27} whereas rifampicin/levofloxacin was antagonistic in a rib cage model of \textit{S. aureus} foreign body infection.\textsuperscript{31} Rifampicin/fluoroquinolone combinations are useful especially for implant-associated infections or osteomyelitis caused by \textit{staphylococci}.\textsuperscript{135} Rifampicin/fluoroquinolone combination therapy was associated with better outcomes than other antibiotic regimens for patients with PJIs due to \textit{S. aureus}.\textsuperscript{36}

In particular, the rifampicin/ciprofloxacin combination is the only regimen whose efficacy has been proven for staphylococcal bone and joint infections associated with stable orthopaedic devices in a randomized comparative trial.\textsuperscript{135} In that study, after initial debridement, either rifampicin/ciprofloxacin combination therapy or ciprofloxacin monotherapy was given after a 2 week intravenous course of fluclaxacillin or vancomycin. The oral therapy lasted for 3 months for patients with hip prostheses and internal fixation devices, and 6 months for patients with knee prostheses. All 12 patients in the rifampicin/ciprofloxacin combination group remained cured after more than 24 months of follow-up. In contrast, only seven (58\%) of the 12 patients in the ciprofloxacin monotherapy group remained cured. Rifampicin-containing combination regimens with ofloxacin and fleroxacin have been evaluated in staphylococcal orthopaedic implant-associated infections,\textsuperscript{121} osteomyelitis associated with diabetic foot ulcers,\textsuperscript{126} and acute bone and joint infections.\textsuperscript{117} One study reported an overall success rate of 74\% after 6–9 months of rifampicin/ofloxacin treatment, with a figure of 62\% in patients without prosthesis removal.\textsuperscript{123}

Rifampicin combinations with newer fluoroquinolones, such as levofloxacin, moxifloxacin or gemifloxacin, have been studied more often than combinations with older fluoroquinolones in bone and joint infections.\textsuperscript{125,126,138–140} The overall cure rates of the rifampicin/levofloxacin combination were 72\% in staphylococcal implant-associated infections\textsuperscript{139} and 96\% in staphylococcal spondylodiscitis.\textsuperscript{140} Considering the antibiotic spectrum and pharmacokinetic/pharmacodynamic characteristics of the newer
<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>Number of patients</th>
<th>Type of infection</th>
<th>Organism (n)</th>
<th>Overall clinical cure rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin/fluoroquinolone</td>
<td>33</td>
<td>orthopaedic device-related infection</td>
<td>MSSA 26, MSSE 5, MRSE 2</td>
<td>100% versus 58%</td>
<td>Zimmerli et al.¹⁵</td>
</tr>
<tr>
<td>Rifampicin + ofloxacin (200 mg tid) for 6–9.months, without removal of the device</td>
<td>47 (evaluable)</td>
<td>orthopaedic device-related infection</td>
<td>S. aureus 26, CoNS 21</td>
<td>74% (81% for hip, 69% for knee and 69% for osteosynthesis device)</td>
<td>Drancourt et al.¹²³</td>
</tr>
<tr>
<td>Rifampicin (600 mg bid) + ofloxacin (200 mg tid) for a median of 6 months</td>
<td>20 episodes in 17 patients with diabetic foot infection</td>
<td>osteomyelitis</td>
<td>monomicrobial 15 + polymicrobial 5, including staphylococci 18</td>
<td>76.5% at a median of 22 months follow-up</td>
<td>Senneville et al.¹²⁴</td>
</tr>
<tr>
<td>Rifampicin (600 mg qd) + levofloxacin (500 mg qd) or moxifloxacin for a median of 7 months (dosage unknown)</td>
<td>11</td>
<td>PJI</td>
<td>S. aureus 5, CoNS 6</td>
<td>91.9%</td>
<td>Soriano et al.¹²⁵</td>
</tr>
<tr>
<td>Rifampicin fusidic acid</td>
<td>20</td>
<td>spondylitis</td>
<td>MRSA 6, MSSA 7, CoNS, others 4</td>
<td>67% in MRSA</td>
<td>Torda et al.¹²⁷</td>
</tr>
<tr>
<td>Vancomycin iv, then rifampicin + fusidic acid for MRSA</td>
<td>46 (23 versus 23)</td>
<td>orthopaedic implant infection</td>
<td>MSSA 5, streptococci 1, MSCoNS 1</td>
<td>86% (6/7) at a 19 month follow-up</td>
<td>Drancourt et al.¹²⁸</td>
</tr>
<tr>
<td>Rifampicin (900 mg qd) + vancomycin (1 g every 12 h) for 2 weeks, then rifampicin (450 mg bid) + ciprofloxacin (750 mg bid) versus ciprofloxacin only for 3–6 months</td>
<td>3</td>
<td>MSSA 26, MSSE 5, MRSE 2</td>
<td>100% versus 58%</td>
<td>Zimmerli et al.¹⁵</td>
<td></td>
</tr>
<tr>
<td>Rifampicin (900 mg qd) + fusidic acid (500 mg tid for 5 days, then 500 mg bid) versus rifampicin (900 mg qd) + ofloxacin (200 mg tid) for 6–9 months, with removal of the prosthesis or implant, if necessary</td>
<td>7</td>
<td>infected orthopaedic implant 4, osteomyelitis 3</td>
<td>MSSA 5, streptococci 1, MSCoNS 1</td>
<td>86% (6/7) at a 19 month follow-up</td>
<td>Drancourt et al.¹²⁸</td>
</tr>
<tr>
<td>a-β-lactam or glycopeptide iv for a median of 12 days, then rifampicin (300 mg bid) + fusidic acid (500 mg tid) for a median of 12 months; all with surgical debridement and prosthesis retention</td>
<td>20</td>
<td>PJI</td>
<td>MRSA 10, MSSA 7, MRCoNS 1, MRSA+MSSA 1, MSSA+MSCoNS 1</td>
<td>90%</td>
<td>Aboltins et al.¹²⁹</td>
</tr>
<tr>
<td>Rifampicin in combination with linezolid</td>
<td>56</td>
<td>infected orthopaedic device 36, chronic osteomyelitis 20</td>
<td>MRSA 21, MSSA 11, MRCoNS 18, MSCoNS 3, others 23</td>
<td>89.3% versus 78.6% (P=0.47)</td>
<td>Nguyen et al.¹³⁰</td>
</tr>
<tr>
<td>Salvage with rifampicin (300 mg tid) + linezolid (600 mg bid) without implant removal</td>
<td>49</td>
<td>PJI</td>
<td>MRSE 22, MRSA 6, culture-negative 17, not described 4</td>
<td>69.4% at a 24 month follow-up</td>
<td>Gomez et al.¹³¹</td>
</tr>
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Table 4. Continued

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>Number of patients</th>
<th>Type of infection</th>
<th>Organism (n)</th>
<th>Overall clinical cure rate</th>
<th>Referencea</th>
</tr>
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<tbody>
<tr>
<td>Rifampicin/SXT (600 mg qd) + SXT (240/1200 mg bid) for 8 weeks versus cloxacillin (iv for 6 weeks, then orally for 2 weeks)</td>
<td>28 versus 22</td>
<td>chronic osteomyelitis (orthopaedic implant 35.7% versus 45.2%)</td>
<td>all MSSA</td>
<td>89% versus 91% at a 10 year follow-up</td>
<td>Euba et al.132</td>
</tr>
<tr>
<td>Rifampicin/ clindamycin (300 mg tid) + clindamycin (600 mg tid) orally for a median of 6 days (0–14 days), then rifampicin (600 mg bid) + clindamycin (600 mg tid) orally for a median of 45 days (35–90 days)</td>
<td>7</td>
<td>PJI</td>
<td>S. aureus 3, CoNS 4</td>
<td>71.4%</td>
<td>Soriano et al.125</td>
</tr>
<tr>
<td>Empirical antibiotics (amoxicillin/ clavulanate, cefuroxime, vancomycin) iv for a median of 6 days (0–14 days), then rifampicin (600 mg bid) + clindamycin (600 mg tid) orally for a median of 45 days (35–90 days)</td>
<td>20</td>
<td>bone and joint infections including implant-associated infections (10)</td>
<td>MSSA 12, MRSA 5, CoNS 3 (co-infection of S. aureus and Streptococcus agalactiae in 1 case)</td>
<td>100%</td>
<td>Czekaj et al.133</td>
</tr>
</tbody>
</table>

bid, twice daily; CoNS, coagulase-negative staphylococci; iv, intravenously; MRCoNS, methicillin-resistant coagulase-negative staphylococci; MRSE, methicillin-resistant S. epidermidis; MScCoNS, methicillin-susceptible coagulase-negative staphylococci; MSSA, methicillin-susceptible S. aureus; MSSE, methicillin-susceptible S. epidermidis; qd, once daily; SXT, trimethoprim/sulfamethoxazole; tid, three times daily.

*Only studies for which the post-treatment follow-up period was more than 1 year are shown.*
ostearticular infections in children and infants in a French guideline. However, it should not be used against bone and joint infections with necrotic tissue because folic acid antagonists do not have synergistic activity against S. aureus in the presence of the elevated thymidine concentrations present in damaged host tissues and fail to prevent the emergence of rifampicin resistance.

(5) Rifampicin/clindamycin combination

Rifampicin/clindamycin was more effective than either agent alone in reducing the bacterial counts in bone in experimental staphylococcal osteomyelitis. Reports of case series have described patients with staphylococcal bone and joint infections, especially implant-associated infections, who were successfully treated with this combination.

(6) Rifampicin/tetracycline combinations

In a rabbit model of orthopaedic device-related infections due to S. epidermidis, rifampicin/minocycline yielded a cure rate of 70%, whereas rifampicin/vancomycin achieved 90% cure. There are several anecdotal cases of staphylococcal bone and joint infections that were treated with rifampicin/tetracycline. The combination of rifampicin with a tetracycline (minocycline or doxycycline) has been recommended in adults with staphylococcal bone and joint infections if there are no other treatment options.

(7) Rifampicin/macrolide combinations

In animal models of staphylococcal osteomyelitis, rifampicin/azithromycin or rifampicin/clarithromycin resulted in reductions of bacterial counts in bone similar to those seen with rifampicin/clindamycin and rifampicin/nafcillin. Based on these data, it is suggested that a rifampicin/macrolide combination can be an alternative oral regimen against staphylococcal bone and joint infections. This still needs to be supported by more clinical experience.

Fluoroquinolone-containing combinations

In vitro studies on staphylococci gave diverse or inconsistent results with combinations of a fluoroquinolone and fusidic acid. Ciprofloxacin/roxofloxacin and clindamycin, gemifloxacin/moxifloxacin and trimethoprim/sulfamethoxazole, ciprofloxacin and tetracycline, moxifloxacin and doxycycline and ciprofloxacin and erythromycin. It has been suggested that a fluoroquinolone/fusidic acid combination could be used against MRSA bone and joint infections if the target organism is susceptible. There is limited clinical experience of bone and joint infections treated with such a combination. Clinical experience with other fluoroquinolone-containing combinations is lacking, except for one example of salvage treatments with the ciprofloxacin/clindamycin combination in staphylococcal bone and joint infections. The value of fluoroquinolone-containing combinations needs to be established as they might be useful when the target organism is not susceptible to rifampicin.

Fusidic acid-containing combinations

Fusidic acid and erythromycin displayed in vitro synergism against staphylococci. A few anecdotal cases have been reported of fusidic acid combined with erythromycin or trimethoprim/sulfamethoxazole for one example of salvage treatments with the ciprofloxacin/clindamycin combination in staphylococcal bone and joint infections. Ideally, the antibiotic used, particularly in implant-associated infections, should have bactericidal activity.
against surface-adhering, slow-growing and biofilm-producing staphylococci.

Investigations revealed that the in vitro results of antibiotic combinations, for example of rifampicin and another antibiotic, often do not correlate with the in vivo findings. Animal studies and models of bone and joint infection have limitations such as a lack of debridement in the animals, high initial inocula, a lack of experience with recurrent or prolonged infection, and the infeasibility of long-term follow-up. These findings and limitations raise a serious question as to whether in vitro or animal studies of the efficacy of antibiotic therapy have sufficient clinical relevance in the treatment of human bone and joint infections. In contrast, human studies, although mostly non-comparative clinical studies or case series, provide limited, but more useful, information on the choice of oral antibiotics in the treatment of staphylococcal bone and joint infections. Based on the available data as described above, we suggest oral agents for the treatment of staphylococcal bone and joint infections in adults, particularly those with chronic/implant-associated infections, as shown in Table 5.

First, rifampicin/fluoroquinolone should be considered as the first-line combination regimen, especially for implant-associated infections, because this combination has been the most extensively studied and its efficacy has been established. Rifampicin/ fusidic acid can be used instead when the isolate is resistant to fluoroquinolones or the patient has adverse reactions to fluoroquinolones. When the aforementioned regimens cannot be used, rifampicin in combination with clindamycin, trimethoprim/sulfamethoxazole, a tetracycline (doxycycline or minocycline) or linezolid can be used. Oral antistaphylococcal penicillins or first-generation cephalosporins can be considered in bone and joint infections caused by methicillin-susceptible staphylococci.

Second, combinations of fluoroquinolones with other antibiotics such as fusidic acid, clindamycin, trimethoprim/sulfamethoxazole or a tetracycline may be considered, but only when treatment fails or severe adverse reactions occur with the aforementioned antibiotic combinations. However, one should keep in mind that there is insufficient clinical experience with these combinations.

Finally, when combinations cannot be employed, monotherapy with a newer fluoroquinolone, clindamycin, trimethoprim/sulfamethoxazole, pristinamycin or linezolid can be tried as a last resort.

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Transparency declarations
None to declare.

References


