Antimicrobial treatment in bone and joint infections

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Abstract

The use of guidelines in infectious diseases is of unquestionable value, especially in non-common conditions, like chronic bone and joint infections. However, in a significant number of these infections it is difficult to apply *one-size-fits-all* treatment strategies, as they will be conditioned by multiple factors, mainly the quality of surgical debridement and residual infection. A basic knowledge of the different phases of the infection and the potential role of antimicrobials at each of these phases will help to make a sensible treatment plan for these particular infections. The initial antimicrobial treatment is usually delivered intravenously but a definitive antimicrobial plan must answer some important questions. The first question is related to the duration of intravenous treatment and appropriateness of switching to oral antimicrobials. Given the limitation on bone penetration of most antimicrobials and the subsequent risk of development of resistance in the presence of suboptimal antimicrobial concentrations, combination therapy is a potential solution, using agents able to perform effectively in the bone, where bacteria usually grow at extremely low rates, limiting the target exposure to some of the most common antimicrobials, which need bacteria actively replicating to inactivate them. A final question is the duration of antimicrobial treatment, which despite the existence of well-defined treatment periods in most of the guidelines, is extremely influenced by the surgical treatment and its capacity to achieve eradication of the infection. In this article we will clarify the above questions.

Keywords antimicrobials; biofilm; bone; infection; rifampicin

The benefit of using *general guidelines* is unquestionable in bone and joint infections. Nevertheless each case possesses specific features, which have to be considered at prescribing antimicrobial treatment. The quality of surgical debridement, local microbiology, patient's clinical condition, drug allergies, potential adverse events and drug-to-drug interactions will undoubtedly influence a definitive antimicrobial treatment.

Biofilm

When treating bone infections, the *biofilm* is a critical aspect to consider. Biofilm is a structured consortium of bacteria embedded in a self-produced polymer matrix. These bacteria remain in a stationary phase of growth (slow-growing or sessile bacteria), hence interfering with the mechanism of action of a significant proportion of antimicrobials, those needing bacteria undergoing replication to activate their target (e.g. β-lactams, glycopeptides). In this regard, rifampicin, with a much better performance against bacteria at this stationary phase, is considered the cornerstone for managing staphylococcal infections associated with biofilm.

However, prioritizing a treatment to target only slow-growing bacteria is a debatable tactic and it is also important to consider treating bacteria in a logarithmic phase of growth (planktonic bacteria), especially in the acute phase of these infections. The use of some antimicrobials judged important for biofilm-associated infections (e.g. rifampicin, fluoroquinolones and co-trimoxazole) in a context of high bacterial inoculum (pre-surgical debridement), increases the chances of drug resistance and may undermine these antibiotics at a later stage in the treatment, when their anti-biofilm activity will be crucial. Rifampin might also have an antagonistic effect on β-lactams and some other antimicrobials with good activity against rapid-growing bacteria, so rifampicin-combination therapy in this setting has to be chosen only after thorough consideration.

Empirical antimicrobial treatment

When considering empirical antimicrobial treatment for bone and joint infections, two main scenarios have to be contemplated.

(1) Acute infections with systemic involvement and an urgent need to start antimicrobials, in order to achieve haemodynamic stability and prevent cartilage damage or the development of a chronic bone infection.
(2) Already established chronic bone and joint infections, with or without flares involving soft tissue.

Individuals belonging to the first group (i.e. septic arthritis, vertebral osteomyelitis, early acute prosthetic joint infections) are usually antimicrobial-naïve patients who may benefit from a narrower spectrum antimicrobial regimen, targeting skin and mucosal bacteria, always considering local microbiology.

Because of the chronic nature of infections in the second group, empiric antimicrobial treatment preceding surgical debridement is usually not needed. However, after surgical debridement, and with the aim to eradicate residual soft-tissue infection, prevent new biofilm formation and protect the new implant, antimicrobial treatment is warranted. Given the significant risk of multi-resistant microorganisms, as previous use of antimicrobials is very common in chronic infections, broad-spectrum empiric antimicrobial treatment is recommended. These regimens usually combine an intravenous glycopeptide with β-lactam antimicrobials, to cover staphylococci, streptococci, enterobacteriaceae and non-fermenting Gram-negative rods. Once the aetiology is known, a tailored specific antimicrobial treatment should be administered.

There is more and more confidence in using oral antimicrobials at the early stages of these infections. Nevertheless, after surgical debridement, most patients would benefit from a short-term course (usually for the first 5–7 days) of high-dose intravenous antibiotics, active against rapidly growing bacteria. Once the dead bone has been debrided, the purulent/necrotic collections removed and soft tissues have begun to settle, it is then time to change to a different group of oral antibiotics, highly bioavailable and with different bacterial targets – the slow growing bacteria embedded within the biofilm.

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Dosing of antimicrobials

Antibiotic dosing should consider the pharmacodynamic profile of antimicrobials, their tissue penetration and the minimal inhibitory concentration (MIC) of the targeted microorganisms. Dosing selection is heavily influenced by the tissue penetration of the antimicrobials being considered. In chronic bone and periprosthetic joint infections, given the poor diffusion of antibiotics within these compartments, the dose of antimicrobials is usually higher than the one exclusively used for soft tissue infections.

Infections caused by *Staphylococcus* spp.

Most available evidence supporting the treatment of staphylococcal infections is obtained from research in *Staphylococcus aureus*, being the treatment of coagulase-negative staphylococci usually based on the extrapolation of data obtained with the former.

Acute phase (bacteria in logarithmic phase of growth)

Meticillin-susceptible *Staph. aureus* (MSSA): the pivotal treatment for MSSA in this setting is flucloxacillin. Ceftriaxone has been advocated as a treatment option in patients with a non-anaphylactic penicillin allergy and for home intravenous antimicrobial therapy, given the convenience in dosing.[1] A retrospective controlled study suggested that ceftriaxone 2 g/day and oxacillin 2 g every 6 hours had similar cure rates.[2] Nevertheless, the clinical evidence available so far is not strong enough to consider both drugs as equivalent. The two most important networks of established experts in the determination of antimicrobial breakpoints and antimicrobial susceptibility testing in the USA and Europe (Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), respectively) have recently eliminated the MIC-based breakpoints for many β-lactams and suggest the use of oxacillin or cefoxitin as surrogate agents for predicting the susceptibility of MSSA to β-lactams, including ceftriaxone.[3] Nevertheless, a recent in vitro pharmacodynamic assessment revealed a marked reduction in ceftriaxone bactericidal activity against *Staph. aureus* when the ceftriaxone MIC was over 2 μg/ml and that the probability of a high ceftriaxone MIC dramatically increased at higher oxacillin MICs (i.e. > 0.5).[4]

We have already mentioned rifampicin as the cornerstone for staphylococcal infections associated to biofilm. In spite of being widely used, there is no substantial evidence favouring the combination of β-lactams with rifampicin, which is supported on very limited clinical studies.[5] On the contrary, there exists in vitro evidence suggesting antagonism between them.[6,7]

Meticillin-resistant *Staph. aureus* (MRSA): for meticillin-resistant *Staph. aureus* (MRSA), vancomycin (aiming for a serum trough level of 15–20 mg/litre) has been the standard of treatment. Teicoplanin (dosing of 12 mg/kg and serum trough level 20–60 mg/litre) is an alternative drug for once-daily dosing to facilitate home intravenous antimicrobial therapy.[8]

The clinical results obtained with the use of glycopeptides in biofilm-associated infections are unsatisfactory, especially in metalwork-retention procedures.[9] In this situation, alternative drugs (i.e. daptomycin, fosfomycin) in combination with β-lactams, may be considered as future options, once further clinical evidence is available.[10]

Recommendations for the acute phase of treatment of staphylococcal bone and joint infections

1. We favour an initial (5–7 days) IV phase of IV flucloxacillin (2 g every 4–6 hours)
2. IV ceftriaxone (2 g once daily) could be used in patients with non-anaphylactic penicillin allergy. A dosage of 2 g twice daily is preferred, to ensure adequate drug levels in *Staph. aureus* bone and joint infections, when the flucloxacillin MIC is 1–2 mg/litre.
3. Rifampicin may be considered along with IV flucloxacillin after an effective surgical debridement, although ceftriaxone-rifampicin combinations are not recommended.
4. To facilitate discharge, after 5–7 days oral treatment is generally preferred over IV ceftriaxone, where optimal oral options for bacteria embedded in biofilm are available (see below).
5. For meticillin-resistant staphylococcal infections, vancomycin (serum trough level 15–20 mg/litre) is still the first choice for the acute phase of treatment, being teicoplanin (dosing of 12 mg/kg and serum trough level 20–60 mg/litre) a useful alternative for ambulatory treatment. Suboptimal outcomes with glycopeptides may prompt the team to consider different alternatives (i.e. combination of daptomycin and fosfomycin with β-lactams) in difficult scenarios. Nevertheless, oral combinations are usually preferred after the initial phase of treatment.

Slow-growing bacteria (bacteria in biofilm)

Rifampicin: rifampicin is considered the cornerstone in the treatment of staphylococcal bone and joint infections, especially in patients with an infected orthopaedic device but, to avoid selecting resistant mutants, it should not be administered in monotherapy. The stronger clinical evidence comes from the combination of rifampicin with fluoroquinolones.[11]

The optimal dosage of rifampicin is unknown. Different regimens (300 mg twice daily, 600 mg once daily, 450 mg twice daily or 900 mg once daily) have been published and current data do not suggest that one regimen is clearly less effective than the others.[12]

Rifampin is known to induce multiple enzymes responsible for drug metabolism and therefore, able to modify the concentration of the accompanying drug needed to provide an effective treatment.

(3) **Fluoroquinolones:** fluoroquinolones are the best studied companion to rifampicin for staphylococcal infections associated with biofilm. A single randomized study demonstrated that monotherapy with ciprofloxacin was inferior to a rifampicin-ciprofloxacin combination, mainly due to the emergence of ciprofloxacin resistance.[11]

Levofloxacin and moxifloxacin are intrinsically more active than ciprofloxacin against *Staph. aureus* and less likely to develop resistance, providing that the bacterial inoculum has been reduced.[13] In a recently published study, monotherapy with high doses of levofloxacin in an experimental model of foreign body-associated staphylococcal infection was superior to the

combination of levofloxacin and rifampicin, with no resistant strains reported.[14] Moxifloxacin, although possessing a higher intrinsic anti-staphylococcal activity, has failed to prove more efficacious than high-dose levofloxacin in experimental models. In addition, rifampin induces the metabolism of moxifloxacin, therefore potentially limiting the usefulness of this combination.[15,16]

Where fluoroquinolones cannot be used, the best alternative rifampicin-based combination is uncertain. Other options include the addition of clindamycin, co-trimoxazole, doxycycline, linezolid, fusidic acid (FA) or pristinamycin.

Co-trimoxazole: bone penetration of co-trimoxazole is suboptimal and previous studies have suggested that high doses of this drug are needed in order to achieve tissue concentrations above the resistance breakpoints for most bacterial pathogens.[17] Moreover, rifampicin reduces the serum concentration of co-trimoxazole by approximately one-third.[18] A combination of co-trimoxazole (7–8 mg/kg/day of the trimethoprim component) and rifampicin has been used as an effective treatment for patients with staphylococcal bone and joint infections.[19] Recent studies reported similar outcomes for this combination, compared with those obtained using linezolid as a partner to rifampicin or IV cloxacillin in monotherapy, for the treatment of bone infections due to *Staph. aureus*.[20–22]

Clindamycin: clindamycin, with a high oral bioavailability and excellent bone penetration, has been successfully used for bone and joint infections caused by staphylococci, either as monotherapy or in combination.[23] Monotherapy with oral clindamycin (20–30 mg/kg/day, divided in three doses) was initially evaluated in the treatment of chronic osteomyelitis in adult patients in the 1970s.[24]

Rifampicin may also interfere with clindamycin serum concentrations (up to a 40% reduction has been documented) however, the clinical importance of this interaction is not clear, since there is no evidence of higher rates of therapeutic failure in patients receiving both antibiotics in combination, provided that clindamycin is used at least at 600 mg three times daily dosing.[25–27]

Linezolid: linezolid has 100% oral bioavailability and reaches high concentrations in musculoskeletal tissues (skin, synovial fluid and bone). A major concern with this antibiotic is, nevertheless, its safety profile. Thrombocytopenia and anaemia may occur, especially in patients receiving linezolid for more than 4 weeks. Irreversible peripheral neuropathy may also occur with prolonged treatment. This safety profile is a major obstacle to a prolonged use in staphylococcal bone and joint infections.

Published data on clinical efficacy do not show significant differences between patients treated with linezolid monotherapy or combined with rifampicin.[28] However, the serum concentration of linezolid may be significantly decreased in the presence of rifampicin and recent evidence suggests that this interaction could be associated with a higher risk of failure.[29–31]

Doxycycline: the use of tetracycline derivatives in the treatment of bone and joint infections is not well reported in the literature. The concentration of doxycycline in bone tissues is not clear, although excellent tissue penetration has been reported by some authors.[32,33] The scarce available clinical data and potential interactions with rifampicin, which again might reduce serum levels of doxycycline, make it difficult to support its use as a first-line combination drug in cases of staphylococcal bone and joint infections.

Fusidic acid: FA has excellent oral bioavailability and achieves good concentrations in soft tissue, bone and synovial fluid. Although there have been no randomized controlled trials of FA as a treatment for bone and joint infections, several case series have reported its effectiveness, mostly in combination with a second antibiotic.[34]

Although the rate of in vitro resistance to FA among *Staph. aureus* is less than 10% in most countries, rates are higher among coagulase-negative staphylococci. A single point mutation is all that is required to generate resistance. Therefore, this agent must be used in combination, rifampicin being the most commonly used drug, to prevent the emergence of resistance. At the same time, rifampicin resistance is responsible for most of the treatment failures associated with this combination, likely associated to insufficient doses of FA which could effectively make rifampicin behave as if in 'monotherapy' and, therefore, some studies have suggested that higher doses than those currently recommended may be more appropriate to avoid rifampicin resistance.[35]

Pristinamycin: to date, pharmacokinetic studies to define the optimal posology of pristinamycin in bone and joint infections have been limited. Pristinamycin at a dosage of 1 g twice or three times daily may be a well-tolerated effective treatment for those infections caused by Gram-positive cocci, in monotherapy or in combination with rifampicin.[36]

The use of pristinamycin in erythromycin and lincosamide (clindamycin) resistant isolates (macrolide-lincosamide-streptogramin B (MLSB) resistance phenotype) should probably be avoided in bone and joint infections if a reasonable alternative is available. This recommendation is based on a recent study in which all three patients with erythromycin and clindamycin-resistant isolates experienced treatment failure.[37] However, the surgical management for these patients was suboptimal, minimizing the role of insufficient antimicrobial dosing in this poor clinical outcome.

Recommendations for the antimicrobial treatment of staphylococcal bone and joint infections at a slow-growing phase (embedded in biofilm)

1. Rifampicin is the 'backbone' of combination therapy for these infections.
2. The best available evidence includes the combination of ciprofloxacin (500–750 mg twice daily) and rifampicin (300 mg twice daily).
3. When rifampicin can not be included at the treatment plan, monotherapy with either moxifloxacin (400 mg once daily) or high-dose levofloxacin (500 mg twice daily) appears to be safe and effective for the treatment of orthopaedic-related staphylococcal infections.
4. Although with unknown clinical relevance, the ability of rifampicin to induce the metabolism of some antibiotics and

therefore reduce their serum concentrations, could lead to the use of clindamycin at 600 mg three times daily and co-trimoxazole 960 mg three times daily, when they are combined with rifampicin.
5. Fusidic acid (500 mg three times daily) has to be used in combination, ideally with rifampicin (300 mg twice daily) to avoid intra-treatment development of resistance.
6. Pristinamycin (1 g twice daily or three times daily) is recommended in multi-resistant staphylococcal infections with limited oral options.

Infections caused by *Streptococcus* spp.

The recommended therapy for streptococcal bone and joint infections relies on β-lactams, at least initially when there is a high burden of replicating bacteria. However, following appropriate debridement, the anti-biofilm profile of β-lactams is questionable as these drugs have poor activity against bacteria in the stationary growth phase. The role of alternative compounds, with a better biofilm profile, has not been consistently explored in clinical studies although recent studies have shown that the addition of rifampicin may improve outcomes. The value of rifampicin combinations, especially with levofloxacin, has been suggested when metalwork is retained (i.e debridement and implant retention procedures in the treatment of prosthetic joint infections).[38]

Recommendations for the treatment of infections caused by *Streptococcus* spp.

1. Acute treatment (planktonic phase): penicillin G 4 MU every 4–6 hours or IV amoxicillin 2 g every 6–8 hours or IV ceftriaxone 2 g every 24 hours.
2. Subsequent treatment (biofilm-embedded bacteria): PO amoxicillin (1 g, three times daily) with or without PO rifampicin (300 mg, twice daily). Alternatives:
   a. PO clindamycin 450–600 mg, three times daily
   b. PO linezolid 600 mg, twice daily
   c. PO levofloxacin 500 mg once daily and PO rifampicin 300 mg twice daily

Infections caused by *Enterococcus* spp.

Amoxicillin is the treatment of choice. However, *Enterococcus* spp are usually tolerant to penicillins (able to persist despite being exposed to concentrations well above the MIC) and monotherapy with these drugs may fail in case of severe infections. The combination with aminoglycosides is synergistic, and this is the reason why it has been traditionally used in severe endovascular infections. Unfortunately, there is no clear benefit of this combination in bone infections, likely due to the poor performance of aminoglycosides in biofilm, with the additional risk of renal toxicity.[39] By contrast, some clinical experience supports the addition of rifampicin or ceftriaxone to amoxicillin.[40]

For patients with penicillin allergy or with penicillin-resistant enterococci, potential alternatives are glycopeptides (in vitro, teicoplanin is one or two dilutions more active than vancomycin against enterococci), linezolid, daptomycin, tigecycline and fosfomycin. The combination of rifampicin with linezolid, daptomycin or tigecycline has revealed the best results in vitro.[41]

Most quinolones display moderate activity toward enterococci, with moxifloxacin exhibiting a good activity in vitro. However, clinical data regarding the use of fluoroquinolones in bone and joint infections due to *Enterococcus* spp remain limited.[42] This lack of clinical evidence also occurs with pristinamycin to which most of the non-*Enterococcus faecalis* species remain susceptible.

Recommendations for the treatment of infections caused by *Enterococcus* spp.

1. The treatment of choice is IV amoxicillin (2 g every 4–6 hours) with or without IV ceftriaxone (2 g, twice daily), followed by PO amoxicillin (1 g, three times daily) with or without rifampicin (300 mg, twice daily).
2. Intravenous teicoplanin, vancomycin, daptomycin and also linezolid and pristinamycin are potential alternatives.

Infections caused by Gram-negative rods

A β-lactam (i.e. amoxicillin, amoxicillin-clavulanate, ceftriaxone…) is recommended during the initial phase of treatment. For subsequent treatment, focused on biofilm-embedded bacteria, ciprofloxacin has demonstrated improved prognosis in the management of peri-prosthetic joint infections and is, therefore, the treatment of choice in all cases of bone and joint infections caused by GNR.[43,44] Where resistance to fluoroquinolones precludes the use of these antimicrobials, β-lactams in monotherapy may be insufficient in this phase of slow-growing biofilm-embedded bacteria and combination therapy along with colistin or fosfomycin may be a therapeutic option, especially dedicated to multi-resistant bacteria.[45] Co-trimoxazole may also has a relevant role at this stage.

Recommendations for the treatment of infections caused by Gram-negative rods

1. For initial treatment (planktonic phase): a β-lactam (a third-generation cephalosporin for enterobacteriaceae, a carbapenem for extended-spectrum β-lactamase (ESBL) or AmpC β-lactamase-producing Gram-negative rods and an anti-pseudomonal β-lactam for *Pseudomonas aeruginosa*).
2. Sequential treatment: PO ciprofloxacin (500–750 mg, twice daily). Alternatives:
   a. Continue treatment with an IV β-lactam with or without colistin or fosfomycin or
   b. Monotherapy with co-trimoxazole.

Culture-negative bone and joint infections

Negative culture results have been reported in most series of bone and joint infections with an incidence ranging from 5% to 25%, recent antimicrobial therapy being the main risk factor.[46] Culture negativity is not necessarily a negative prognostic factor, although it definitely interferes with an optimal antimicrobial management by hampering the choice of drugs, creating difficulting decisions on the delivery route and challenging the antimicrobial management in patients with drug-related side effects.[47]

The presumed microbiology of patients with culture-negative bone and joint infections is similar to that of those patients with an identified microorganism. In this situation, it seems reasonable to administer antimicrobials with a comparable

spectrum to previous antibiotic regimens, considering combination therapy to diminish resistance barriers. These decisions should be always guided by the local microbiology of each hospital.

Recommendations for the treatment of culture-negative infections

1. The use of antibiotics prior to a valid sampling should be avoided if possible, at least for 2 weeks.
2. The antimicrobial treatment must be active against the most prevalent microorganisms, also considering previous significant microbiology, clinical condition and epidemiological context.
3. Combination therapy must be considered.

Recommendations for treatment duration in different scenarios

The optimal duration of the antimicrobial treatment for bone and joint infections is not known and remains under ongoing debate. Surgical debridement is a critical element, which undoubtedly influences the final duration of antimicrobial treatment.[48,49]

The following recommendations constitute a general guidance that needs to be adjusted by microbiology, host status and soft tissue management. A better understanding of local antimicrobial therapy will probably reduce the length of current treatment duration recommendations.

1. Non-implant-associated chronic osteomyelitis
   a. Optimal surgical debridement: 4–6 weeks
   b. Suboptimal surgical debridement: 8–12 weeks
2. Implant-associated chronic osteomyelitis with implant retention
   a. Early infection: 12 weeks
   b. Late infection: until metalwork removal
3. Peri-prosthetic joint infection
   a. Debridement and implant retention (DAIR): 12 weeks versus 6 months (the longer course dedicated to knee joints and *Staph. aureus* infections)
   b. Single stage reimplantation: 8–12 weeks
   c. Two-stage reimplantation: 6 weeks after first-stage (explantation)

Conclusions

In spite of the indisputable role of clinical guidelines, the antimicrobial management of chronic bone and joint infections merits an individualized approach, due to its complicated nature and elevated risk of treatment failure if any element is suboptimal, taking into account that the clinical outcome is strongly related to the quality of the surgical debridement.

It is extremely important to possess a deep knowledge of the several phases of the process of infection and the interactions of the different antimicrobials with the potential responsible organisms at each of these stages, with the aim to establish an optimal treatment plan for the specific case.

Following an exhaustive surgical debridement, a short course of intravenous antimicrobials, based on β-lactams if microbiologically appropriate, is used with the aim to clear a potential bloodstream infection and treat the soft tissues. This is followed by oral antimicrobial treatment, selected on the basis of its ability to penetrate a biofilm environment and target the responsible bacteria, isolated after a protocolized intraoperative sampling process.

The ultimate duration of antimicrobial treatment will be heavily influenced by the surgical treatment and the theoretical efficacy of the antimicrobial in that particular environment. Given the recalcitrant nature of these infections, combination therapy with antibiotics highly effective against biofilm-related infections (i.e. rifampicin) is usually recommended. ◆

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