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Antibiotic treatment of Gram-positive bone and joint infections

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Gram-positive organisms, particularly staphylococci and streptococci, are responsible for the majority of bone and joint infections. Treatment of these infections can be difficult, usually involving a prolonged course of antibiotics, often with surgical intervention. The selection of antibiotics depends on sensitivity profile, patient tolerance and long-term goals, e.g. cure or suppression, but there are few randomized controlled trials in patients comparing efficacy of different antibiotics. Different degrees of bone penetration and clinical outcome for specific antibiotics, e.g. the β-lactams, clindamycin and quinolones, have been described, although the methodology in these studies is not standardized and findings cannot always be applied directly to patients. The effect of attaining minimum serum bactericidal concentrations in patients has also been studied but this is no longer routinely recommended in clinical practice. Comparative clinical trials are few but have demonstrated efficacy of oral fluoroquinolones in combination with either rifampicin or fusidic acid for selected Gram-positive infections. In the past decade, increasingly resistant organisms, e.g. methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci have been recognized as causes of orthopaedic infection. Individual case reports describe successful treatment using the newer antibiotics, e.g. linezolid and quinupristin/dalfopristin, but results of clinical trials are awaited.

Keywords: staphylococci, streptococci, osteomyelitis, septic arthritis, prosthetic joint infections

Introduction

Gram-positive organisms are responsible for the majority of bone and joint infections. Bone infection, at sites of relatively poor vascularity, can be difficult to treat, often requiring prolonged courses of antimicrobial therapy in association with surgical drainage or debridement. Delayed or ineffective treatment causes significant morbidity in terms of pain, loss of function and the need for further surgery and antibiotics. Selection of the most appropriate systemic antibiotic therapy will therefore need to reflect the organism(s) isolated and sensitivity profile, pharmacokinetic factors such as penetration into bone, presence of prosthetic material, vascular supply of the affected limb and the patient's individual tolerance of the drugs. (The use of antibiotic impregnated cement or beads will not be discussed in this review.)

Causal organisms in bone and joint infection

Staphylococcus aureus is the single most common organism causing osteomyelitis[1,2] and septic arthritis.[3,4] Coagulase-negative staphylococci (CoNS) are more prevalent in prosthetic joint infection (PJI) followed by *S. aureus*.[5] β-Haemolytic streptococci are also responsible for bone infection, e.g. Lancefield group B osteomyelitis in neonates and group A septic arthritis in other age groups. Enterococci are recognized causes of PJI[6] as are non-haemolytic and viridans streptococci. In contrast, *Streptococcus pneumoniae* is a relatively rare cause of septic arthritis and raises the question of underlying immunosuppression[7] as does *Listeria monocytogenes*, a rare cause of PJI.[8,9] Anaerobes may contribute to polymicrobial osteomyelitis in vasculopathic infection[10] such as diabetic foot infection and in septic arthritis following animal bites.[11] Gram-negative organisms are responsible for a low proportion of all bone and joint infections although particular patient groups are predisposed to specific Gram-negative infections. Prior to the introduction of the Hib vaccine, for example, *Haemophilus influenzae* was a major cause of septic arthritic joint in children of pre-school age but this is now a much rarer cause while *Neisseria gonorrhoea* may be responsible for septic arthritis in young adults. Gram-negative bone and joint infection will not be discussed further in this review.

Osteomyelitis

The Cierny–Mader classification of osteomyelitis, which takes account of site of infection, source of infection and patient health status has been described elsewhere.[12] More simply, osteomyelitis

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can be described as 'acute or chronic' and 'haematogenous or contiguous', according to the duration and source of infection, respectively. The extent of bone involvement is described as medullary, superficial localized or diffuse (i.e. stages 1–4) depending on the depth of infection and extent of bone destruction. The presence of underlying vascular disease and the age of the patient (adult or child) also affect the management and prognosis, both in terms of time to heal and penetration of antibiotics. Traditionally, adult osteomyelitis has necessitated ≥6 weeks parenteral therapy to gain adequate concentrations in a site of relatively low vascularity with necrotic bone and sequestrum. Some studies on the use of oral β-lactams in adults have been published,[13,14] but the majority report success in paediatric osteomyelitis,[15–19] which heals much more rapidly than in adults. The role of oral antibiotics in the treatment of bone infection is discussed below.

Osteomyelitis in paediatric patients is usually haematogenous in origin and mainly occurs in the long bones. The vascular supply of the developing bone facilitates early spread of medullary infection to the epiphysis, which may result in septic arthritis of the proximal joint. The highly vascular nature of developing bone and very effective response to bone infection means children can often be managed with shorter courses of antibiotics with early switch to oral therapy often without need for surgical excision.[20,21]

Septic arthritis

Septic arthritis of a native joint is most commonly caused by *S. aureus* followed by Lancefield group A β-haemolytic streptococci as a consequence of direct trauma or haematogenous spread.[3] Causal pathogens in particular age groups largely mirror those for osteomyelitis. Polymicrobial infection is not usual but may be anticipated following penetrating injuries including animal bites. Antibiotics are usually commenced after drainage of the affected joint. Synovial penetration of most antibiotics is generally good but with slower and lower peaks in synovial fluid compared with serum concentrations.[22–24] Aminoglycosides are less active in synovial fluid (and in bone).[22] Penetration of flucloxacillin and cefradine, used frequently to treat septic arthritis, was disappointing in one study,[24] but the selected intravenous (iv) doses were lower than would normally be used and the subjects used did not have an acutely infected joint so penetration was not necessarily comparable. Direct intra-articular instillation of antibiotics is not necessary and not recommended.[21,25] The duration of treatment is not clearly evidence based but typically 2–3 weeks for uncomplicated infection is appropriate,[26] though this need not be parenteral throughout.[22] In summary, synovial fluid concentrations of most antibiotics are good in septic arthritis if given in adequate dosage and direct administration is not necessary.

Prosthetic joint infection

PJI is fortunately a relatively uncommon complication following hip and knee joint replacement (incidence approximately <1% and 0.5%, respectively[27]) but can require prolonged therapy and often necessitates removal of the affected prosthesis.[28–30] The management approach is more akin to that of chronic osteomyelitis than that of septic arthritis. Infection may occur early or late, from direct intra-operative inoculation, wound infection or haematogenous seeding. The most common pathogens implicated are CoNS followed by *S. aureus*,[3] but almost any organism may be implicated including enterococci, streptococci, corynebacteria, Enterobacteriaceae and anaerobes.[5] Several organisms may be isolated from infected material, leading to confusion about the individual relevance of each;[31] the collection of multiple specimens is advocated to determine the significance of those considered possible contaminants.[32] Antibiotics directed at all significant pathogens are required, ideally those with good activity against adherent bacteria and those producing a biofilm,[33] e.g. rifampicin or one of the fluoroquinolones. PJI requires antibiotic treatment for ≥6 weeks to several months in addition to surgery.[34] Chronic suppression with long-term antibiotics has been used as a 'last resort' when further surgery has not been possible.[29]

Traditionally it has been understood that the effective treatment of deep-seated bone infection necessitates a prolonged course of parenteral antibiotics. Alternatives to lengthy hospitalization for parenteral antibiotic therapy have evolved, including Outpatient and Home Parenteral Antibiotic Therapy schemes,[35–38] but also the increasing use of oral antibiotic agents that have both acceptable bone penetration and high oral bioavailability. This review will consider antibiotics available and appropriate for therapy of Gram-positive osteomyelitis and joint infection.

Antibiotic choices: general points

The relatively high failure rate following antibiotic treatment of bone infection is well documented. Risk factors for poor outcome include inadequate initial debridement, the presence of prosthetic material, duration of infection and previous treatment failure.[39] Chronic osteomyelitis and PJI are particularly difficult to cure and it has been suggested that 'arrest' is a more appropriate term than 'cure' for effective outcome in chronic osteomyelitis as relapse may occur many months or years later.[40]

The initial choice of antibiotic inevitably depends on the causal pathogen and its sensitivity pattern. Antibiotics considered bactericidal against the infecting organisms are often considered necessary (the logic being similar to that of treating infective endocarditis or meningitis), although the need for this with respect to osteomyelitis has not been experimentally proven. Measurement of peak and trough serum cidal ratios to guide dosing has been advocated. In a study by Weinstein *et al.*,[41] trough serum bactericidal titres of >1:2 and >1:4 for acute and chronic osteomyelitis, respectively, accurately predicated cure in 48 cases of osteomyelitis (average follow-up 40 months). Use of serum cidal titres to guide dosing has been reported in other studies of bone and joint infection[17,19,34] but the selection of titre appears somewhat arbitrary.[42] The effect on outcome of deliberately maintaining a dose despite lower titres has not been compared. With the difficulties in performing serum bactericidal tests and the generally poor reproducibility of 'in house' results,[43] serum bactericidal tests are probably not helpful in the routine management of osteomyelitis.

Ideally all dead or diseased bone should be removed surgically at the earliest opportunity and this is the gold standard of treatment; however, this is not always possible and even when early debridement is aggressive it takes 3–4 weeks for adult bone to revascularize. As a result areas of poor penetration and low oxygen tension may exist at the site of infection. Anaerobiasis at the site of deep infection may adversely affect the activity of antibiotics, for example gentamicin (which has good bone penetration) and vancomycin, while it does not affect activity of rifampicin and cephalosporins.[44,45]

Antibiotic bone penetration and clinical studies

Bone penetration of many antibiotics has been studied,[46–48] but interpretation of the results is difficult as methodology has not been standar-

dized and therefore results have varied. For example, blood contamination has been accounted for in some studies but not in others, some report antibiotic concentrations in diseased bone which are higher than those measured in healthy bone, likewise penetration into cortical bone varies significantly from that measured in medullary bone and finally assay procedure can account for considerable variations in results. Animal studies have offered insight into the management of bone infection in terms of comparative efficacy and bone penetration. Limitations of these trials, however, include lack of debridement in the animals, high initial inocula and lack of experience with recurrent or prolonged infection. Similarly, long-term follow-up is not possible in experimental models. *S. aureus* is invariably chosen as the infecting organism to study anti-Gram-positive agents, which reflects many, but not all, cases in patients; results cannot therefore be directly applied to streptococcal or CoNS infection. The significance of peak bone concentrations in relation to the MIC for the isolate is not fully understood and this and the clinical outcome in animal studies do not always correspond. Despite these limitations though, useful information about antibiotic bone and serum concentrations, time to sterilization and percentage cure has been published. Studies of the more commonly used antibiotics for bone and joint infection will be discussed.

β-Lactams and lincosamides

Cefalothin has been studied by several investigators: Norden *et al.*[49] found no detectable levels in rabbit bone 2 h after subcutaneous injection in contrast to lincomycin which produced detectable levels. Against *S. aureus* osteomyelitis, lincomycin was more effective in sterilizing bone at 14 days but after 28 days there was no difference between the two. Smilack *et al.*[47] found no detectable cefalothin (and no penicillin) in hip bone at 0.5 and 2 h after a single injection in patients with uninfected hips, but found significant uptake of methicillin, clindamycin and carbenicillin. In contrast, in a similar study Fitzgerald *et al.*[23] compared bone penetration of cefalothin, methicillin and oxacillin measured in excised hip 1 h after injection and found no significant difference between bone concentrations. He commented that more patients given cefalothin attained bone concentrations of >1 μg/g than those given oxacillin or methicillin, and concluded that cefalothin was superior for bone prophylaxis. However, the MICs for *S. aureus* were exceeded by all three antibiotics in bone at the time of excision, so the significance of attaining 1 μg/g is questionable as it does not appear to relate to clinical outcome. Cefuroxime and cefamandole are often used as prophylaxis for orthopaedic procedures. In a study of patients undergoing non-infected hip replacement, a similar degree of bone penetration, 38–44%, was demonstrated in patients receiving a prophylactic dose of either cefuroxime or cefamandole. At 30 min post-dose a mean bone concentration of 29.6 and 13.1 mg/L was measured following a dose of 1.5 g cefuroxime or 1 g cefamandole, respectively.[50] These data illustrate the difficulties in interpreting single studies in isolation with respect to antibiotic bone penetration. In contrast to cephalosporins, clindamycin exhibits consistently high penetration in bone[49,51–53] and in synovial fluid[54] in the presence of relatively low serum concentrations. Using pharmacokinetic modelling with infected rats, Gisby *et al.*[52] demonstrated >494% peak penetration of clindamycin compared with 10% and 21% for co-amoxiclav and flucloxacillin in homogenized bone. In this study, treatment with co-amoxiclav and clindamycin gave the highest rates of sterilization at 28 days versus *S. aureus* although flucloxacillin had been administered at a comparatively low dose for reasons of tolerability. Using rabbits, clindamycin gave both higher mean bone concentrations and greater microbiological efficacy than 15 mg/kg cefazolin against *S. aureus*. At 30 min post-infusion, bone concentrations of both antibiotics exceeded the MIC for the organism despite lower serum concentrations of clindamycin.[53] Schurman[55] demonstrated higher cortical bone concentrations and bone:serum ratios in patients undergoing (sterile) total hip replacement following three doses of clindamycin (concentration 3.8 μg/g ratio 0.45) compared with three doses of methicillin (concentration 2.6 μg/g ratio 0.22). Clinical superiority could not be judged, as there were no postoperative infections in either group. In a study of similar design, bone concentrations were measured after marrow had been removed. Bone concentrations of 2.6 μg/g were recorded with a mean bone:serum ratio of 0.4.[56] Some of the discrepancies between assay results in these studies reflect the effect of active metabolites of clindamycin measured in bioassay and the assay of whole bone rather than bone stripped of marrow. Dornbusch *et al.*[51] confirmed that, using different methods to assay clindamycin in bone, e.g. agar diffusion wells, paper discs and electrophoresis, within the same study group, different results are produced making it difficult to compare the findings of individual studies. Clindamycin, with both good bioavailability and high bone:serum ratios is an ideal choice for switch therapy in patients who no longer require hospital admission. In children it has been shown to be comparable to standard parenteral therapy.[16,18] Concerns about an association with pseudomembranous colitis have limited its use in elderly patients, but it should be borne in mind that such patients are also at risk of developing *Clostridium difficile* diarrhoea while receiving other parenteral antibiotics, such as cephalosporins.

In the UK flucloxacillin is commonly used for first-line therapy of deep *S. aureus* infection. Bone concentrations of between 0.9 and 1.3 mg/L flucloxacillin have been achieved corresponding to bone:serum rations of 0.12–0.16 following a single dose of 0.5–1 g prior to hip replacement.[57] By exceeding the MIC for sensitive *S. aureus*, Unsworth *et al.*[57] concluded that 1 g flucloxacillin offered effective prophylaxis when given 2 h prior to hip excision but the spectrum of cover might now be considered rather narrow for total hip replacement. Other reports have demonstrated bone concentrations of oxacillin and methicillin, the preferred anti-staphylococcal penicillins used in other countries, to be in excess of the MIC following iv injection to subjects undergoing joint replacement. Bone:serum ratios of 0.18–0.22 and 0.11 for methicillin and oxacillin, respectively, were reported and are comparable to those for flucloxacillin above.[23,55] Clinical success was reported in 44 patients treated with iv, followed by oral, co-amoxiclav for chronic bone infections following debridement or surgery. Serum and bone concentrations were not measured. Follow-up was limited to 12 months, at which time all had clinical cure or improvement with one relapse and one infection;[58] however, follow-up of <2 years is generally considered too short to determine efficacy in chronic osteomyelitis. Furthermore, in the absence of comparative trials there appears no reason to treat *S. aureus* with co-amoxiclav rather than flucloxacillin unless patient tolerance is a problem, but the additional Gram-negative and anaerobic cover is useful for polymicrobial infection.

Quinolones

The fluoroquinolones, e.g. ciprofloxacin, ofloxacin and pefloxacin have been studied extensively in bone and joint infection and offer some anti-Gram-positive activity *in vitro*. Quinolones have an effect on adherent bacteria, penetrate macrophages and polymorphs,[59] exhibit high bone:serum concentrations after oral administration[60]

and have a low side-effect profile. The bone concentrations achieved are proportional to the dose administered[60] and are in excess of the MICs for the majority of infecting organisms after one dose, i.e. >1 μg/g bone. Following repeated does of pefloxacin, bone concentrations of between 2 and 10 μg/g (0.7–0.6 mg/L) were achieved[61] and bone:serum ratios of >7.3 have been reported after a single dose of ciprofloxacin.[62] The efficacy of these quinolones against Gram-positive osteomyelitis is impressive and compares well with standard therapy. There are several excellent reviews of trials of quinolone in bone and joint infections, which summarize encouraging results in studies including Gram-positive, Gram-negative and polymicrobial infections.[63–65] Gentry *et al.*[66] reported effective outcome in 8/8 patients with staphylococcal infection [excluding methicillin-resistant *S. aureus* (MRSA)] compared with failure in 2/8 in the 'standard' parenteral therapy and Mader *et al.*[67] showed that ciprofloxacin was as efficacious in polymicrobial chronic osteomyelitis as standard therapy although all three recurrences after ciprofloxacin were caused by Gram-positive organisms identified on the original culture. Ofloxacin (which has MICs comparable to those of ciprofloxacin but achieves higher serum concentrations) has been compared with 'standard' parenteral therapy for chronic osteomyelitis. After 8 weeks, in those treated for staphylococcal infection there were three relapses out of 10 in the ofloxacin group compared with none out of six in the other group. Relapses were attributed to selection of resistant staphylococci during treatment.[68] Increasing resistance amongst *S. aureus* has been observed since the introduction of quinolones,[69] and has resulted in the addition of rifampicin to attempt to prevent this occurring during treatment. An overall success rate of 74% for patients treated was observed with 6–9 months oral rifampicin and ofloxacin for implant-related staphylococcal infection.[70] In the face of increasing *S. aureus* resistance to quinolones, ofloxacin plus rifampicin was compared with fusidic acid plus rifampicin in a similar study.[70] Although there was no significant difference between the two groups in terms of outcome, the cure rate in the ofloxacin–rifampicin group was only 11/22 (50%) compared with a cure rate of 74% in the preceding study. Amongst failures rifampicin resistance was very common. In addition, 5/6 failures in the ofloxacin group were resistant to ofloxacin; in contrast, in the fusidic acid group only one of the six failures was resistant to fusidic acid. However, it could not be proved whether resistant isolates were those present (but not detected) from the outset or acquired during treatment.[71] This highlights the importance of being able to accurately identify all significant pathogens (and be confident that contaminants are only contaminants) at the start of treatment. Comparing pefloxacin monotherapy and combination therapy with rifampicin for staphylococcal infection, Desplaces & Acar[60] observed three treatment failures in 20 patients due to resistant organisms in the monotherapy group but none in 13 treated with pefloxacin plus rifampicin.

More recently, newer quinolones have been introduced, e.g. moxifloxacin and levofloxacin, which have lower MICs than ciprofloxacin *in vitro* for Gram-positive organisms.[72] Studies on their use in respiratory tract infection have been published particularly with respect to *Streptococcus pneumoniae* but data on penetration and efficacy in bone infection and use against other Gram-positive pathogens are not yet available. The safety of the newer quinolones in long-term use and the existence of any cross-resistance to older quinolones will need to be established.

Currently available quinolones therefore offer an attractive and effective alternative to standard parenteral therapy for sensitive Gram-positive infections. The possibility of acquired resistance must be considered and the use of a second agent in the treatment of *S. aureus* infection is advisable.

Rifampicin and fusidic acid

The effect of rifampicin in combination with various antibiotics has been very encouraging in clinical trials despite *in vitro* synergy and time–kill studies, which might appear to contradict this.[73–75] It is particularly useful in eradicating bacteria adherent to prosthetic material in joint infection or chronic osteomyelitis. A mean bone concentration of 1.7 μg/g was recorded in rabbits with osteomyelitis 1 h post-injection, corresponding to a serum concentration of 6.4 mg/L. Rifampicin has excellent anti-staphylococcal activity and bioavailability, can penetrate white blood cells to kill phagocytosed bacteria and can eradicate adherent organisms in the stationary phase making it the (almost) ideal antibiotic for bone infection. It has been shown to be particularly successful as an adjunct to oral ciprofloxacin in PJI or osteomyelitis with metal pins *in situ*.[76] Rifampicin with nafcillin was compared with nafcillin alone in the treatment of chronic osteomyelitis. After 2–4 years follow-up, four of eight patients treated with nafcillin alone had a favourable outcome compared with 8/10 treated with the combination. The numbers were too small to be significant but the authors concluded that the addition of rifampicin to nafcillin is useful in the management of persistent staphylococcal infection.[77] The use of rifampicin is limited by the rapid development of resistance and must therefore be combined with a second agent. Some patients are unable to tolerate rifampicin due to side effects or drug interactions. Hepatic failure has been reported with use of fusidin and rifampicin combinations for MRSA[78] so monitoring of liver function is advisable. Rifampicin has been used in combination with penicillins and cephalosporins,[73,76,79] with quinolones[70,71,79] and with vancomycin, teicoplanin or minocycline for MRSA.[45,80,81]

Fusidic acid, like rifampicin, reaches high intracellular concentrations and has good activity against *S. aureus.* Bactericidal concentrations have been attained in infected bone and penetration of sclerotic bone and sequestra has been demonstrated in the presence of high serum concentrations.[82,83] As with rifampicin, resistance to fusidic acid (which may be reversible) develops rapidly if it is not used in combination with a second agent.[83]

Antibiotics used to treat MRSA bone infection

Methicillin-resistant staphylococci were first detected within a year of the introduction of methicillin but have become increasingly prevalent in the last 20 years. The glycopeptides, vancomycin and teicoplanin have become the mainstay of treatment in the UK for MRSA infection. Individual preferences for one or the other vary although it is considered by some that vancomycin offers superior treatment for staphylococci with more rapid killing due to lower protein binding than teicoplanin.[84] Against this, vancomycin cannot be given by bolus injection, unlike teicoplanin, and has a higher association with nephrotoxicity at high serum concentrations.[85] High-dose and prolonged therapy with teicoplanin has been associated with thrombocytopenia and neutropenia, particularly when pre-dose concentrations exceed 60 mg/L.[86] In animal studies, vancomycin alone has been ineffective at sterilizing infected bone and combination with rifampicin has shown varying success. In a study using rats the combination was not more effective than was rifampicin alone. Mean bone:serum ratios measured for vancomycin were 0.13, and the combination of ciprofloxacin and rifampicin was most effective although vancomycin and rifampicin was more effective at prevent-

ing later re-growth of *S. aureus*.[87] In contrast, Norden found the vancomycin–rifampicin combination to be between 84% and 90% effective at sterilizing infected bones of rabbits after 14 and 28 days therapy, respectively. Mean peak bone concentrations of vancomycin reached 8.4 μg/g compared with a serum concentration of 57 mg/L. Synergy was not demonstrated *in vitro* or in time–kill studies.[44] It was suggested that the poor outcome for vancomycin could be attributable to decreased activity in anaerobic conditions.[44,87] In patients, vancomycin concentrations and bone:serum ratios in uninfected bone are lower than for other antistaphylococcal agents. After 15 mg/kg, bone:serum ratios of 0.13 and 0.07 in cortical and cancellous bone, respectively, were achieved but mean bone concentrations exceeded the MICs for the isolates in most cases.[88] Sheftel *et al*.[89] reported the use of vancomycin (with tobramycin for polymicrobial infection) in treatment of MRSA. After 6 weeks therapy there were two failures and five successes. In the case of failures the vancomycin MICs measured after treatment were higher than at the outset. Nephrotoxicity occurred in both patients given the combination. Fitzpatrick *et al*.[90] reported use of vancomycin in 10 patients with MRSA osteomyelitis. The duration of vancomycin ranged from 10 to 46 days and a proportion of pre-dose concentrations measured, were lower (range 1–12 mg/L) than currently recommended. All four failures occurred in patients with associated foreign body, two of which had remained *in situ*. The pre-dose concentrations of these failures were not reported.

Teicoplanin has been particularly useful, enabling patients to be discharged from hospital while continuing with parenteral therapy as it can be given by bolus injection once daily or less frequently.[36,91,92] Bone concentrations of a mean of 65% serum concentrations have been measured 3 h post injection during cardiac surgery.[93] A summary of non-comparative studies ($n = 23$) has demonstrated between 50% and 100% efficacy for bone infections (median success rate 83%),[94] although this would incorporate the initial studies using lower doses with decreased efficacy. While streptococcal infections are particularly amenable to treatment with teicoplanin,[95] higher doses to give high trough serum concentrations appear necessary to treat deep-seated staphylococcal bone infection.[36, 92,96–98] Le Frock *et al.*[99] used doses of 6–12 mg/kg to treat bone and joint infection in 90 evaluable patients. After an average of ~6 weeks therapy for osteomyelitis and 3 weeks for septic arthritis, cure rates were 90%, 88% and 100% for acute and chronic osteomyelitis and septic arthritis, respectively. The reasons for selection of higher doses for some osteomyelitis patients in this study were not clear; 12 mg/kg is recommended for septic arthritis.

Oral minocycline (with and without rifampicin) has been shown to be useful in the treatment of MRSA infection, including osteomyelitis.[74,80,100,101] Despite combination with a second agent, rifampicin resistance has emerged with the combination and whether the combination is actually superior to minocycline alone has been questioned.[74] High-dose oral co-trimoxazole has also been used to treat MRSA implant infection as an alternative to glycopeptides. After prolonged high-dose therapy the overall cure rate at 6 years was 66.7% but side effects were a cause for cessation in eight patients.[102] (The use of quinupristin/dalfopristin and linezolid for MRSA infection is discussed below.)

New antibiotics

The appearance of vancomycin-resistant enterococci (VRE) and glycopeptide-intermediate *S. aureus* (GISA) as causal pathogens in orthopaedic infection has challenged clinicians and microbiologists to find new antibiotics or combinations effective in deep infection but also tolerable over prolonged courses.[103] Synercid is the proprietary name of a streptogramin consisting of quinupristin and dalfopristin, and is a bactericidal antibiotic that inhibits protein synthesis by binding to the 50S ribosome subunit.[104] It has activity against *Enterococcus faecium*, including vancomycin-resistant strains and *S. aureus* (including MRSA). It is not active against *E. faecalis*.[104] Quinupristin/dalfopristin must be administered via central line in dextrose infusion three times daily; the most troublesome side effect is myalgia, which may necessitate cessation. In a study of 40 patients treated for MRSA bone and joint infections (mean duration 42 days), clinical and bacteriological success was observed in 77.5% and in 69% of those evaluable.[105] There is also reported success in the treatment of single cases of VRE osteomyelitis of the vertebra[106] and the foot,[107] although in the latter case outcome was not reported beyond a few weeks post-cessation of antibiotics. Using a rabbit model of PJI with MRSA, improved outcome and more rapid killing was demonstrated with the combination of quinupristin/dalfopristin and rifampicin compared with vancomycin and rifampicin.[108] Caution must be used if a *Staphylococcus* sp. is resistant to erythromycin as, due to cross-resistance of the MLS_B type, this antibiotic may be only inhibitory, but not cidal. Organisms with an MIC of ≤2 mg/L are considered susceptible.[109] Finally, the most recent addition to the armamentarium licensed in the UK is linezolid, an oxazolidinone. Bacterial protein synthesis is inhibited by binding of a specific site on the 50S ribosomal subunit. Linezolid represents a new class of antibiotic with no cross-resistance to other antibiotics. It is licensed in the UK for the treatment of soft tissue infection and pneumonia and is active against Gram-positive organisms including VRE (*E. faecium* and *E. faecalis*) and MRSA. Organisms with an MIC of ≤4 mg/L are considered susceptible.[109] In contrast to quinupristin/dalfopristin, linezolid can be given by peripheral infusion and orally has 100% bioavailability.[110] While it appears promising in other fields there are few published data on the treatment of bone infection although linezolid concentrations measured in bone samples from 10 individual patients ranged from 3.3 to 17.4 mg/kg, mean 8.5 mg/kg.[111] It has potential to interact with other drugs, e.g. monoamine oxidase inhibitors and may cause reversible anaemia or thrombocytopenia with continued use. At present it is not recommended for more than 28 days; however, there are anecdotal reports of longer use, under careful observation, without adverse effect. Successful treatment for MRSA has been reported in two cases of osteomyelitis,[109] one of vertebral osteomyelitis[113] and in a case of VRE PJI.[114] In contrast, results were poor in an animal study comparing 25 mg/kg twice daily linezolid given intraperitoneally twice daily or thrice daily with cefazolin 50 mg/kg given intramuscularly thrice daily for *S. aureus* osteomyelitis, with no difference in outcome between linezolid and the control group.[115] As linezolid offers one of the only options for oral treatment of some of the most resistant Gram-positive organisms, results of further studies are keenly awaited.

Conclusions

In conclusion, Gram-positive infection accounts for the majority of bone and joint infections. Antibiotics penetrate well into the synovial fluid of infected joints and following drainage, treatment of septic arthritis can be achieved with 2–3 weeks iv and oral therapy. Penetration of antibiotics into bone is more variable and dependent on several factors. Treatment of osteomyelitis and PJI requires weeks to months of antibiotic therapy in addition to removal of all infected material. Traditionally, parenteral antibiotics have been advocated for the

whole course to achieve acceptable bone concentrations. High bone penetration of some antibiotics, notably the fluoroquinolones and clindamycin, enable early oral switch therapy for some patients; for this group oral antibiotic therapy should be considered an effective and appropriate alternative to exclusively parenteral therapy. Ultimate choice of antibiotic, use of oral therapy and duration of course will be governed by microbiological, surgical and patient factors and should be discussed on an individual patient basis with the clinician and medical microbiologist. The presence of increasingly resistant infecting organisms is a concern, both in terms of managing the affected patient and the wider cross-infection implications. The efficacy of the 'new' antibiotics has yet to be demonstrated in orthopaedic infection although preliminary reports are encouraging.

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