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Review Article

Newer antibiotics for musculoskeletal infections

Dilip Pawar[1], Prasan Bhandari[2]

INTRODUCTION

The management of bone and joint infections like osteomyelitis, septic arthritis, and prosthetic joint infections (PJI) can often be painstaking as in a wide majority of them. Gram-positive organisms such as *Staphylococcus* species and *Enterococci* are the prime culprits. Surgical management including debridement along with prolonged antibiotic course is necessary especially for bone infections with relative poor vascularity. Repeated surgical procedures and antibiotic course are associated with delayed or ineffective treatment in the case of significant morbidity in the form of pain and loss of function. Sensitivity of the organisms isolated, presence of prosthetic material, the local vasculature, pharmacokinetic aspects of the antibiotic (especially its bone concentration), and drug tolerance are the factors which govern the selection of the appropriate antibiotic to treat such patients.[1]

Causal organisms

The single most common offending agent for osteomyelitis and septic arthritis is *Staphylococcus aureus*.[2–5] PJI is frequently caused due to coagulase-negative staphylococci (CoNS) followed by *S. aureus*.[5] Bone infection could also be caused by beta-hemolytic streptococci especially in neonates. Enterococci, non-hemolytic streptococci, and *Streptococcus viridans* are the causative organisms for PJI; however, in immunocompromised situations *S. viridans*[6] and rarely *Listeria monocytogenes*[7,8] could also account for PJI's. In diabetic foot infections and animal bite-induced septic arthritis, polymicrobial infection including anaerobes may be responsible.[9] Hemophilus influenza was one of the common cause for septic arthritis in pre-school age children prior to the introduction of hiB vaccine. Very rarely are Gram-negative organisms the cause. Hence treatment aspects for the same will not be discussed further.

Osteomyelitis

Treatment and prognosis of such conditions is governed by the presence of underlying vascular disease and the age of the patient, especially in relation to the duration of healing and penetration of antibiotics. Conventionally, adult osteomyelitis required more than 6 weeks of parenteral therapy to achieve requisite concentrations in a poorly vascularized site along with necrotic bone and sequestrum. Oral beta lactams are more effective in pediatric osteomyelitis, as compared to adults, as is the rate of healing.[10–16]

Septic arthritis

The organisms responsible for septic arthritis are similar to those causing osteomyelitis namely *S. aureus* and beta hemolytic streptococci.[4] Adequate drainage of the affected joint followed by antibiotic therapy is the usual course of treatment. The rate and speed of penetration of the antibiotics in the synovial fluid though adequate is slower and lower *vis-à-vis* its serum concentrations.[17,18] Flucloxacillin and cefradine are used commonly to treat septic arthritis.[19] Aminoglycosides are less active in the synovial fluid.[17] Studies do not recommend the direct intra-articular instillation of antibiotics.[17–21] Approximately 2–3 weeks of antibiotics may be necessary, though such evidence is inconclusive.[17]

Prosthetic joint infections (PJI)

This complication which is not commonly seen subsequent to hip and knee joint replacement might necessitate long-term treatment and removal of prosthesis.[22–24] In this regard the management is similar to that of chronic osteomyelitis. Organisms commonly causing PJI's are coagulase negative *S. aureus* (CoNS) followed by *S. aureus*. However, organisms like streptococci, enterococci, enterobacteriaecae, and

[1]Director & Head, Clinical Development (India), Dr Reddys Laboratory Limited Hyderabad – 500090, [2]Associate Professor, Department of Pharmacology, SDM Medical College, Sattur, Dharwad, Karnataka.
Correspondence: *Dilip Pawar, email: dilippawar@hotmail.com*

anaerobes may also be responsible.[5] Keeping in mind the possibility of contaminants, it is advisable to collect multiple samples.[25] Only the causative pathogens should be treated, especially adherent bacteria and those producing biofilm[26] with rifampicin or fluoroqinolones. Besides surgical management, antibiotics treatment for more than 6 weeks to several months could be necessary.[27] However, in conditions where surgery is not possible, long-term antibiotics for chronic suppression may be tried as a last resort.[28]

Selection of antibiotic therapy

It is generally well accepted that antibiotic therapy is associated with a relatively high failure rate. Past history of treatment failure, duration of treatment, presence of prosthetic material, initial inadequate debridement, are all risk factors for negative prognosis.[29] Since relapses may occur in the future, especially in patients with chronic osteomyelitis and PJI, it has been suggested that "palliation" rather than "cure" should be an effective practical outcome expected.[30] The causative organism and its sensitivity pattern should govern the choice for the initial antibiotic treatment. As far as possible agents with bactericidal activity against the infecting pathogens should be utilized. Dosing should be based upon the measurements of the peak and trough serum cidal ratios.[14,16,20] However, the selection most often is empirical.[31] Whenever and wherever possible, the gold standard of treatment, that is removal of all the dead and diseased bone surgically, at the earliest, should be followed. Despite these measures, it requires approximately 3–4 weeks for an adult bone to revascularize. Hence, areas with inadequate penetration and less oxygen tension may persist at the site of infection. The generation of anaerobic infection may negatively impact the effects of antibiotics like gentamicin and vancomycin, however, preserving the activity of rifampicin and cephalosporins.[32,33]

Beta lactams and lincosamides

Cephalosporins such as cephalothin, cefuroxime, and cefamandole have been used frequently for bone prophylaxis.[18,34] In a study conducted by Gisby et al.,[35] treatment with clindamycin and co-amoxiclav gave the highest rates of sterilization at 28 days *vs*. *S. aureus*. Clindamycin with advantage of good oral bioavailability and high bone: serum ratios, is the preferred choice for switch therapy especially for patients to be subsequently treated on an outpatient basis. In children it has been shown to be comparable to standard parenteral therapy.[13,15] Elderly patients could develop clostridium difficile-induced diarrhoea or pseudomembranous colitis following these antibiotics, a point to be kept in mind. Flucloxacillin, oxacillin, and methicillin are some commonly used anti-staphylococcal penicillins in subjects undergoing joint replacement.[18,36,37] However, in addition, Gram-negative and anaerobic cover is beneficial for polymicrobial infection.

Quinolones

Extensive *in vitro* studies have demonstrated the role of fluoroqinolones like ciprofloxacin, ofloxacin, and pefloxacin against some Gram-positive organisms. They are advantageous in terms of efficacy against adherent bacteria, penetration into macrophages and polymorphs[38] high bone: serum concentrations following oral administration[39] and concentrations more than MIC's of the majority of the offending pathogens.[40] Promising results have been demonstrated in several trials especially against Gram-positive, Gram-negative, and polymicrobial infections.[41–43,63–65] However, the widespread use of quinolones has led to the emergence of quinolone-resistant *S. aureus* strains.[44] Addition of either rifampicin or fusidic acid has improved the scenario, albeit, to a certain extent.[45] Thus, it is imperative to identify all the significant causative organisms, differentiating from the contaminants, at the initiation of treatment. The availability of newer quinolones like moxifloxacin and levofloxacin confers theoretical advantage of having lower MIC's as compared to the older generation agents like ciprofloxacin against Gram-positive organisms. Additionally, the long-term safety and existence of any cross resistance to older quinolones needs to be evaluated.[46]

Rifampicin and fusidic acid

Combination of rifampicin with various antibiotics has shown promising outcomes in several clinical trials; however, certain *in vitro* synergy and time-kill studies have demonstrated contradictory results.[47–49] It is especially beneficial in chronic osteomyelitis and PJI, due to the ability to eradicate adherent bacteria. Additionally, its ability to penetrate white blood cells to kill phagocytosed bacteria, good bioavailability, excellent anti-staphylococcal activity, makes it an ideal choice for bone infection. Particularly, its combination with oral ciprofloxacin in patients with chronic osteomyelitis or PJI has been successful *in situ*.[50] However, its utility could be limited due to the development of resistance, inability to tolerate due to side-effects, and frequent drug interactions. Of particular concern is hepatic failure, hence frequent monitoring of liver functions is recommended. Rifampicin has been evaluated in combination with penicillins and cephalosporins,[47,50,51] quinolones[45,51,52] vancomycin, teicoplanin, or minocycline for MRSA.[33,53,54]

High serum concentrations, bactericidal levels in infected and sclerotic bone, good intracellular concentrations, and

good activity against *S. aureus* are some of the advantages of fusidic acid.[55,56] Like rifampicin, early development of resistance, is one of the prime limitations of fusidic acid, unless used with combination.[56]

Antibiotics for MRSA bone infection

The problem of MRSA infection has emerged as early as 1 year since its introduction, and has continued to be so till date. Although individual variations do occur in their choice of treatment, vancomycin and teicoplanin has been the mainstay of treatment in the UK, rapid killing of staphylococci and lower protein binding are some of the advantages of vancomycin over teicoplanin.[57] However, nephrotoxicity and inability to administer as bolus, could restrict the usage of vancomycin.[58] Similarly the ability of teicoplanin to cause dose-dependent thrombocytopenia and neutropenia should be borne in mind.[59]

Additionally, vancomycin has poor bone penetration and some animal studies have demonstrated an inability to sterilize bone.[60,61] Increased prevalence of vancomycin-resistant *S. aureus* (VRSA), vancomycin-resistant enterococci (VRE) are already limiting its usage.[62–65] An increased risk of recurrence seen with vancomycin treatment of *S. aureus*[66] additionally restricts its usage.

The first parenteral streptogramin, that is Quinopristin-Dalfopristin (Q-D), is effective in approximately two thirds of patients with MRSA infections. In addition, its combination with rifampicin was significantly more effective than monotherapy in a preclinical trail of knee MRSA infection.[67] The frequently encountered side effects included arthralgia, myalgia, and nausea.[68] However, Q-D is not indicated for bone/joint infections since limited clinical data is available in this setting.[69]

Linezolid, an oxazolidinone, a new class of antibacterial agent, is particularly effective against Gram-positive infections, including methicillin and vancomycin-resistant strains.[70] The FDA has approved both oral and intravenous formulations for the treatment of various infections including complicated or uncomplicated skin and soft tissue infections, with or without associated osteomyelitis caused due to *S. aureus*.[71]

Long-term safety and efficacy data needs to be produced in bone and joint infections, since they are lacking. Additionally, no large randomized trials have been published on the use of linezolid for orthopaedic infections. Adverse events reported with the use of linezolid include anemia and peripheral neuropathy.[72] Early identification of linezolid associated peripheral neuropathy is imperative since this may be irreversible.[73] Resistance to linezolid too has been reported among strains of MRSA and *Enterococcus faecium*.[68,74,75] Its potential to interact with other drugs such as monoamine oxidase inhibitors, too should be kept in mind. Attention should be paid to adverse effects that may be related to linezolid administration, especially bone marrow suppression with prolonged administration of the antibiotic.

Tigecycline, the first glycylcycline approved in the United States, is indicated for complicated skin soft tissue infections and complicated intra-abdominal infections, but not for orthopeadic infections. It has activity against both methicillin susceptible and methicillin resistant *S. aureus*. Although there have been no human trials involving osteomyelitis, animal studies do suggest its role in orthopaedic infections treatment. Commonly reported adverse events include nausea, vomiting, diarrhea, local IV site infection, and fever.[76,77] Resistance to tigecycline has been reported among both Gram-positive and Gram-negative organisms.

MRSA osteomyelitis could also be treated with oral minocycline either alone or in combination with rifampicin.[48,33,78,79] High dose of oral co-trimoxazole too has been useful as an alternative to glycopeptide.[80]

Additionally, nasal decolonisation with mupirocin may be a rational strategy to reduce the risk of hematogenous implant-associated infection. Mupirocin nasal ointment should be considered in patients colonized with methicillin-resistant *S. aureus* (MRSA) who undergo non-emergency orthopeadic procedures. In addition, such patients should be strictly isolated in the hospital and their intervention should be planned as the last of the day.

Daptomycin, is a novel cyclic lipopeptide with bactericidal activity against Gram-positive bacteria including MRSA and VRE. This bactericidal action is caused due to the disruption of multiple bacterial plasma membrane functions, without penetrating the cytoplasm.[81] Insertion of the lipophilic daptomycin tail into the bacterial cell membrane causes rapid membrane depolarization and potassium ion efflux. Arrest of DNA, RNA, toxin production and protein synthesis follows, resulting in bacterial cell death without cell lysis.[82–84] Daptomycin was approved in the year 2003 for the treatment of complicated skin and soft tissue infections caused by *S. aureus* (including methicillin-resistant strains), *S. pyogenes*, *S. agalactiae*, and *E. faecalis* (vancomycin susceptible strains only) at a dose of 4 mg/kg/day given parenterally. In 2006, daptomycin as once daily therapy (6 mg/kg) was approved for the treatment of *S. aureus* bacteremia, caused by MSSA and MRSA.[81] Daptomycin appears to be effective against multi-drug resistant Gram-positive organisms commonly found in osteomyelitis and joint infections even when the other first-line drugs have failed.[81] However, no randomized and controlled trials comparing the effectiveness and safety of daptomycin with other antibiotics used to treat bone and joint infections have been completed.[73]

Daptomycin is well tolerated with a low potential for adverse events, and a risk of spontaneous resistance appears low.[83,85] Daptomycin has been largely used as a salvage therapy following vancomycin failure.[86,87] The novel mechanism of action, rapid *in vitro* bactericidal activity against growing and stationary-phase bacteria, a once-a-day dosing regimen, and no requirement of drug monitoring, may contribute to its potential therapeutic advantage.

New immunotherapies, exploitation of novel antibiotic targets, topical therapies, and new drug delivery systems may have a future role in the management of *S. aureus* infection. Five anti-Gram-positive agents (moxifloxacin, quinupristin-dalfopristin, linezolid, daptomycin, and tigecycline) have become available to tackle this infection. In addition three more antimicrobial agents (ceftobiprole, gemifloxacin, and iclapri) are to be introduced and a further four (ceftaroline, dalbavancin, oritavancin, and telavancin) have completed phase III clinical trials

CONCLUSIONS

Gram-positive infections account for the majority of orthopaedic infections. Treatment of septic arthritis includes drainage, along with 2–3 weeks of parenteral and oral antibiotics with adequate synovial fluid penetration. Removal of the infecting material along with weeks to months of antibiotic therapy remains the mainstay in the treatment of chronic osteomyelitis and PJI. Fluoroquionolones and clindamycin have the ability to achieve good and high bone concentrations. The choice of antibiotic, route, and duration depends upon the patient, microbiological, and surgical factors and should be discussed individually as well as jointly. The increasing menace of resistance is a concern both for the clinician and the patient as well. Most of the new agents are pharmacodynamically promising and effective in clinical trials. As in the past, drug safety is likely to be a major determinant of which of the most recent drugs receive regulatory approval, and, in the long term, which agents will be successful in clinical practice.

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