Prosthetic joint infections: single versus combination therapy

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Prosthetic joint replacement is used increasingly to alleviate pain and increase mobility. Bone and joint infections remain a therapeutic dilemma for healthcare providers in all fields. Antimicrobial agents combined with appropriate surgical techniques play a vital role in eradicating infections associated with prosthetic joints. The question still remains whether monotherapy or combination therapy is effective in this situation because there is a paucity of well-defined comparative studies. We reviewed in vitro and in vivo studies evaluating the effectiveness of various antimicrobial agents either as single agents or in combination.

Keywords: PJI, synergy, antagonism, antimicrobial combinations, time–kill experiments, bioavailability, pharmacokinetics, biofilms

Antimicrobial combinations: general principles

Antimicrobials are normally used as single agents to treat most human infections, but there are some clinical conditions where a combination of antimicrobials may be indicated. When two antimicrobial agents are combined, they may have one of three effects in vitro against the organism: additive or indifferent; synergy; or antagonism.1 The main clinical indications for combination therapy are prevention of emergence of resistant organisms, polymicrobial infections, as initial empirical therapy, to decrease dose-related toxicity, and synergy. Synergy has been demonstrated when penicillinase-resistant semi-synthetic penicillins are combined with gentamicin against Staphylococcus aureus.2 When compared with nafcillin alone, the combinations of nafcillin/gentamicin and nafcillin/tobramycin significantly increased the number of organisms killed during the first 6 h of incubation.

Similarly, antipseudomonal penicillins may exhibit synergy when combined with aminoglycosides against strains of Pseudomonas aeruginosa.3 Although there are definite benefits in combining antimicrobial agents, there are also a few limitations such as antagonism, cost, and increased adverse effects.

Introduction to prosthetic joint infections (PJIs)

PJIs are one such condition where combinations of antimicrobial agents are frequently prescribed. Some of the combinations used include flucloxacillin/rifampicin, ciprofloxacin/rifampicin, vancomycin/rifampicin, cefepime/cefazidime + aminoglycoside,3 ampicillin/gentamicin,4 teicoplanin/gentamicin5 and levofloxacin/rifampicin.6

Prosthetic joint replacement is used increasingly to alleviate pain and improve mobility. Though occurring in only 1%–2% of total joint replacements, PJIs are associated with significant morbidity. This in turn accounts for a substantial proportion of hospital expenditure. Treatment of an infected prosthetic joint may be ~US$15000–US$50000 per episode.5 Owing to the absence of well-designed prospective, randomized, controlled studies with appropriate follow-up, treatment choices for PJIs are largely based on tradition, personal experience and other factors. This in turn leads to differences in practice between institutions. Also, the different specialists involved in the management of this complication, such as orthopaedic surgeons, infectious diseases specialists and microbiologists, may have different approaches.

PJIs are typically caused by microorganisms that grow in biofilms, which are protected from antimicrobials and host immune responses. Biofilm-associated bacteria play a very vital role in antimicrobial resistance as they are 100–1000 times less susceptible to antibiotics than planktonic bacteria.

Therefore, the frequency of PJIs appears to be increasing and the management of these infections remains a therapeutic dilemma.

Treatment

Treatment of PJIs includes a combination of surgical interventions and antimicrobial therapy. The management of these infections is less standardized due to variable clinical presentations and lack of randomized controlled trials.3,4 The goal of treatment is to eradicate infection in order to achieve a pain-free functional joint. Exchange arthroplasty in one or two stages and aggressive resection of all infected tissue is the mainstay of management.

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Another strategy is debridement with implant retention and long-term suppressive antimicrobial therapy active against biofilm microorganisms. The former procedure continues to be the standard approach in the management of infected prostheses due to higher cure rates compared with the latter.

When choosing an antibiotic, ideally it should be bactericidal against surface-adhering slow-growing biofilm-producing microorganisms, and have good oral bioavailability and penetrate bone and joint tissues. Rifampicin, clindamycin, co-trimoxazole, quinolones, fusidic acid and linezolid have excellent bioavailability when given orally in bone infections. Teicoplanin or vancomycin and rifampicin may be appropriate options in the presence of methicillin-resistant S. aureus (MRSA). There is a paucity of clinical data for the treatment of Gram-negative bacilli. In vitro and animal studies have demonstrated better efficacy of ciprofloxacin against Gram-negative bacilli than β-lactams.

**Monotherapy versus combination therapy**

It is not clearly understood whether either monotherapy or combination therapy is better for eradication of bacteria in PJI. There have been a few studies on combination antibiotics, most of which involve rifampicin. Quinolones are excellent combination agents because of their bioavailability, antimicrobial activity, tolerability and long-term efficacy in bone and joint infections.

In clinical scenarios where long-term antibiotic therapy is indicated rifampicin plays an important role. It has all the qualities needed to treat biofilm organisms, it can be taken orally, is active against S. aureus and MRSA, and has excellent bioavailability and tolerability (expect in hepatic impairment). Its effectiveness has been proven in vitro, in animal models, and in clinical studies, with >50% cure rate. It cannot be used as a single agent in staphylococcal infection due to rapid development of resistance through a single point mutation in DNA-dependent RNA polymerase. Rifampicin must therefore be administered with another antistaphylococcal agent with similar pharmacokinetic properties. Recent BSAC guidelines for treatment of MRSA bone and joint infections recommend use of parenteral glycopeptides with or without adjunctive agents such as rifampicin or sodium fusidate as initial therapy. There is no evidence that a single agent or combination is superior.

**Combination antimicrobials against Gram-positive organisms**

**Fluoroquinolone/rifampicin**

When used as monotherapy quinolone resistance among staphylococci species is reported at 35%. A quinolone/rifampicin combination is potentially very effective because it eliminates device-related staphylococci and also prevents the emergence of ciprofloxacin resistance. It is fairly well tolerated, can be given orally and both achieve high intracellular concentrations. In a single prospective randomized double-blind placebo-controlled trial, Zimmerli et al. concluded that orthopaedic device-related infections due to rifampicin- and ciprofloxacin-susceptible staphylococci can be cured without removal of the device if the implant is stable, the duration of infection is <3 weeks, initial debridement is performed and the patient can tolerate long-term antibiotics. The trial compared two treatment approaches both intended to salvage the implant. They observed that 3–6 months systemic therapy with ciprofloxacin/rifampicin had a cure rate of 100% compared with 58% with ciprofloxacin monotherapy. Most failures were due to ciprofloxacin resistance during therapy. Barberon, in a prospective cohort study with a combination of levofloxacin/rifampicin, showed clinical and bacteriological success rates in the range of 69.5%–80% in patients with a short duration of symptoms (≤1 month). According to Widmer, rifampicin should always be considered in staphylococcal infection if susceptible in vitro. Oral ofloxacin/rifampicin combination showed a success rate of 74% after treatment for 6–9 months for implant-related staphylococcal infection. Failures in this study were due to ofloxacin or rifampicin resistance. Pefloxacin was also effective when used in combination when compared with monotherapy. Currently there are no clinical data available for rifampicin combinations with other quinolones such as moxifloxacin and gemifloxacin which have much lower MICs for staphylococci.

**Rifampicin/fusidic acid**

As seen with rifampicin, fusidic acid also has various characteristics which make it a suitable combination agent, since it achieves high intracellular concentrations, has good activity against S. aureus with bactericidal concentrations in infected bone, and penetrates into sclerotic bone and sequestra in the presence of a high serum concentration. It also has limitations such as rapid development of reversible resistance when used as a single agent and high risk of hepatic failure when used in combination with rifampicin.

Drancourt et al. in a non-randomized clinical trial showed a success rate of 55% with rifampicin and fusidic acid when used in combination. Oral therapy of staphylococcal infection of orthopaedic implants with 900 mg/day rifampicin combined with either 1.5 g/day fusidic acid for 5 days, followed by 1 g/day thereafter, or 600 mg/day ofloxacin were compared. Patients with an infected hip were treated for 6 months, with removal of any unstable prosthesis after 5 months treatment, and those with an infected knee prosthesis were treated for 9 months, with removal of the prosthesis after 6 months of treatment. Patients with infections of other types of bone implants were treated for 6 months, with removal of the implant after 3 months of treatment, if necessary. Cure was defined as the absence of clinical, microbiological and radiological evidence of infection 12 months after completion of treatment. Overall treatment was successful for 11 (55%) of 20 patients treated with rifampicin/fusidic acid and for 11 (50%) of the 22 treated with rifampicin/ofloxacin. Treatment failed in four cases in each treatment group because of persistent infection. The authors concluded that rifampicin/fusidic acid combination may be a good alternative to ofloxacin/rifampicin for treating staphylococcal implant infection.

Other antibiotics used in combination with rifampicin include β-lactams, glycopeptides, linezolid, co-trimoxazole, minocycline and clindamycin. A retrospective cohort study was conducted of 40 consecutive episodes in 35 patients undergoing surgery for prosthetic knee infection. In that study 23 patients treated with long-term (3 months) rifampicin-containing combination had a success rate of 95.7%, which compared with the rates of 86% and 100% reported by other studies.
Teicoplanin/rifampicin compared with vancomycin

The prophylactic and therapeutic activities of teicoplanin were evaluated in two different experimental models of foreign body infections caused by MRSA. Whereas high levels of teicoplanin were found in tissue cage fluid, continuously exceeding its MBC for MRSA by 8- to 16-fold, no significant reduction in the viable counts of MRSA occurred during therapy. In contrast, either vancomycin alone or a combined regimen of high-dose teicoplanin/rifampicin (25 mg/kg twice daily) significantly decreased the viable counts in tissue cage fluids. The altered susceptibility of in vivo growing bacteria to teicoplanin killing might in part explain the poor activity of this antimicrobial agent when used as monotherapy against chronic S. aureus infections. Therefore, if teicoplanin is used it must be combined with another agent such as rifampicin to optimize the therapy of severe staphylococcal infections, or used at a higher dose such as 12 mg/kg.

Linezolid as a single agent versus combination with rifampicin

Bassetti et al. looked at use of linezolid as a single agent in Gram-positive PJI. This was a retrospective evaluation of patients with the diagnosis of Gram-positive PJI and treated with intravenous and/or oral linezolid monotherapy. Twenty patients were treated for an overall duration of 6–10 weeks. At long-term follow-up (1 year) four patients failed due to relapsing infections. The remaining 16 patients did not need further surgical interventions and no drug-related adverse events were recorded. Linezolid has a good pharmacokinetic profile and achieves high concentrations in osteoarticular tissue. Fifteen patients had previous antibacterial therapy with a combination of rifampicin/ciprofloxacin (11) or glycopeptides (4). An important advantage of linezolid is oral administration. Potentially there may be cost savings when linezolid is used as it can be given orally, but data are only available for complicated skin and soft tissue infections (cSSTIs). As the haematological effects were detectable through weekly monitoring and were reversible, the authors concluded that concerns about myelosuppression do not preclude its use for long-term therapy and that it is an effective agent when used as monotherapy. In the treatment of suspected or proven Gram-positive infections, results of a randomized controlled, open label study showed that linezolid is clinically superior though less well tolerated than teicoplanin. From a safety perspective various adverse events have been reported following prolonged therapy (14–28 days), including neuropathy (peripheral or optical), haematological abnormalities (particularly thrombocytopenia or anaemia) and hyperlactataemia.

Linezolid/rifampicin

Murillo et al. tested the in vitro and in vivo antibacterial efficacy of linezolid alone and in combination with rifampicin in a rat model of foreign body infection by methicillin-susceptible S. aureus using cloxacillin as a comparator drug. In vitro experiments were performed against bacteria in both the log and stationary phases. Significant observations from this study are outlined as follows. Cloxacillin/rifampicin showed antagonism in the log phase and indifference in the stationary phase. The combination of linezolid/rifampicin showed indifference in both phases and no antagonism with different antibiotic concentrations. Neither combination achieved bactericidal activity against non-growing bacteria. Linezolid offered protection against development of rifampicin resistance. Linezolid monotherapy was significantly worse than rifampicin alone and rifampicin combinations. The efficacy of linezolid/rifampicin increased over time, thus maintaining the benefits of rifampicin. The authors concluded that linezolid and cloxacillin showed only moderate efficacy in this model of foreign body infection with S. aureus, whereas its combination with rifampicin prevented the emergence of rifampicin resistance. Linezolid displays non-bactericidal, time-dependent activity in vitro on staphylococci. Resistance to linezolid has been reported after treatment for at least 3 weeks with S. aureus strains.

Jacqueline et al. used time–kill experiments to measure bactericidal activities of antibiotics when used in combinations. Linezolid and gentamicin are both ribosome-targeted compounds. The formation of an initiation complex is crucial for the bactericidal activity of aminoglycosides. By preventing the formation of an initiation complex linezolid could block this critical site of action for gentamicin. In time–kill curves the combination appears to be antagonistic mainly for the early bactericidal activity of gentamicin. Rifampicin, by binding to DNA-directed RNA polymerase, prevents elongation of the RNA chain and stops bacterial growth. When used in combination rifampicin normally acts before linezolid in the ribosome cycle during the first 6 h, but linezolid takes over on RNA polymerase-mutated bacteria by acting later in the ribosome cycle. Thus linezolid and rifampicin seemed to be the most active combination against MRSA strains in time–kill experiments. However, in vivo studies are required to validate these observations. Gebhart et al. have reported a possible interaction between linezolid and rifampicin in a critically ill patient leading to decreased serum linezolid levels.

Quinupristin/dalfopristin and vancomycin/rifampicin

The efficacies of quinupristin/dalfopristin 30 mg/kg 8 hourly and vancomycin 60 mg/kg 12 hourly alone or in combination with rifampicin 10 mg/kg 12 hourly were compared in a rabbit model of MRSA knee prosthesis infection. The use of rifampicin with quinupristin/dalfopristin or vancomycin increased the killing rates of both quinupristin/dalfopristin and vancomycin by 2 log_{10} cfu at 6 h in each case, and this increase was sustained for the full 24 h of incubation. Vancomycin monotherapy failed to sterilize bone in any animal and did not significantly reduce the mean bacterial count in bone. Quinupristin/dalfopristin monotherapy sterilized infection in only 1 of 12 animals but did produce a significant reduction in bacterial count. However, the combination of rifampicin/quinupristin/dalfopristin led to bone and prosthesis sterilization of all animals tested. Rifampicin resistance emerged during combination therapy with vancomycin but not with quinupristin/dalfopristin combination.

Vancomycin alone and in combination with rifampicin and tigecycline

Rose and Poppens evaluated vancomycin susceptibility and activity alone and in combination with rifampicin/tigecycline.
against clinical isolates of MRSA producing biofilm. Susceptibilities were determined in planktonic and biofilm cultures using microbroth dilution. Time–kill analysis was performed with 15 mg/L vancomycin alone and in combination with the above antibiotics at 4× the MIC. Strains were classified as low or high biofilm producers based on optical density measurements. Vancomycin did not achieve bactericidal concentrations against the latter. As single agents neither rifampicin nor tigecycline at 4× the MIC was effective at reducing inoculum, but when vancomycin was combined with either agent they achieved bactericidal concentrations against all isolates, including high biofilm producers. The conclusion was that rifampicin reduces bacterial adherence in biofilms, thus improving vancomycin activity.

**Daptomycin**

Daptomycin is a novel cyclic lipopeptide which has been shown to have in vitro bactericidal activity against antibiotic-resistant Gram-positive bacteria such as MRSA, glycopeptide-intermediate S. aureus (GISA) and glycopeptide-resistant enterococci (GRE). It has rapid concentration-dependent bactericidal activity irrespective of growth phase, and no cross-resistance with other classes of antimicrobials has been reported. In vitro studies have demonstrated daptomycin to be significantly more effective than linezolid and vancomycin in inhibiting and eradicating MRSA in biofilm. Hence it has some attractive properties for targeting microbial organisms involved in chronic or foreign body infections. In the rat model of chronic foreign body infections due to *S. aureus*, daptomycin showed in vivo efficacy equivalent to that of vancomycin, with significant reductions in the bacterial burden. It was also demonstrated that high tissue levels may be required to prevent the emergence of subpopulations exhibiting decreased susceptibility. Synergy between daptomycin and both rifampicin and β-lactams was found against vancomycin-resistant enterococci (VRE) and MRSA in vitro, but the efficacy of this combination in vivo is not known.

**Antimicrobial combinations against Gram-negative organisms**

**Ceftazidime/ciprofloxacin**

In the study by Brauqui et al., ceftazidime 1.5 g twice a day and oral ciprofloxacin 500 mg three times a day were given in combination for 6 weeks, followed by oral ciprofloxacin to treat *P. aeruginosa*-infected implants. The indwelling devices included one hip prosthesis, four knee prostheses and nine percutaneous traction pins or plates. Therapy failed in one patient and the rest were cured without implant removal after a mean follow-up of 21 months. Ceftazidime alone had a cure rate of 91.7% for 48 patients with bone and joint infections.

**Antagonism**

Antagonism between antimicrobial agents is a well-established phenomenon. As early as 1951 Lepper and Dowling, from fatality rates, showed that penicillin (rate 21%) is more effective as a single agent than combination of penicillin and chlorotetracycline (rate 79%) for the treatment of pneumococcal meningitis. Similarly Mathies and associates showed a statistical difference in mortality between children treated with ampicillin alone and those treated with ampicillin combined with chloramphenicol and streptomycin. Although there are reports on in vitro antagonism, there are not many reports of similar mechanisms in vivo. This raises the question of the clinical significance of these results. The above-mentioned interactions occur at a subcellular level when the antibiotics act on a given organism. The other type of interaction known is the one that occurs between the drugs before they reach the microorganism. Some examples are chloramphenicol/erythromycin which form insoluble precipitates if used in the same parenteral infusion, and carbencillin/gentamicin where aminoglycosides may be inactivated in patients with severe renal failure.

**Discussion**

There is a paucity of large clinical multicentre trials comparing the role of monotherapy versus combination antibiotics in the treatment of PJIs. Time–kill experiments tend to favour use of antibiotic combinations especially with respect to glycopeptides and linezolid. Our current practice is, where possible, to choose an agent which is active against biofilms. Since the majority of these agents may result in resistance if used as monotherapy, we add a second agent.

Conventional antimicrobial testing is normally aimed at planktonic or free-growing bacteria; however, this may not necessarily reflect susceptibilities of the same organisms when they are grown as biofilms. Isolates grown planktonically and as biofilms were tested against combinations of antimicrobial agents. Rifampicin, vancomycin and fusidic acid were the antibiotics most commonly used in combinations. Rifampicin emerged as the single most active agent with bactericidal activity, confirming previous studies. Sanginur et al. concluded that biofilms were generally insensitive to individual antimicrobials compared with combinations. In vitro biofilm susceptibility testing may be a futuristic guide for the selection of appropriate antibiotics in PJIs. Caution should be exercised when selecting antibiotics in certain high-risk groups due to the potential risks of *Clostridium difficile*-associated diarrhoea. With the increasing use of prosthetic devices to treat complicated osteoarticular issues, there is also an emergence of multiresistant Gram-negative infections. Would the use of synergistic antibiotic combinations improve outcome in these cases? There are no well-defined studies to either prove or disprove this.

**Conclusions**

From anecdotal reports, observational and in vitro studies, it can be concluded that rifampicin may be an effective combination antimicrobial agent in the treatment of biofilms associated with *S. aureus*. Not many antibiotic combinations have been tested other than rifampicin and fusidic acid, and as such we have limited data to state conclusively that combination therapy is better than monotherapy in the treatment of PJIs.

**Transparency declarations**

None to declare.
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