G77: What is the optimal antimicrobial treatment for patients with multidrug-resistant implant related infections?

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Response/Recommendation:

The selection of antimicrobial therapy to treat multi-drug resistant organisms should consider patient comorbidities, mode of administration, risk of *Clostridioides difficile*-associated diarrhea, need for drug monitoring, allergy profile of the patient, intolerance, regional resistance patterns, cost and availability. Ideally, antibiotics should also provide good bone and soft tissue penetration and anti-biofilm activity. Expert consultation with infectious diseases specialists and clinical microbiologists is strongly recommended.

Strength of recommendation: Limited

Delegate Vote:

Rationale:

This question remains inadequately addressed in the current literature. Of the 2,095 articles screened, 57 were deemed relevant, primarily consisting of level IV clinical series, literature reviews, and case reports. However, these studies often lacked details on the therapeutic regimens used, and frequently reported treatment failures. While numerous *in vitro* studies show promise, clinical validation is lacking. Treatment success rates for PJI caused by resistant pathogens are lower than those for susceptible organisms, leading to higher morbidity and costs (29).

Biofilms confer relative resistance even to susceptible antimicrobials, particularly in debridement and implant retention (DAIR) cases. The selection of antimicrobial therapy should consider not only the minimum inhibitory concentration (MIC) but also, in research settings, the minimum biofilm-eradication concentration (MBEC) and minimum biofilm bactericidal concentration (MBBC), if available. Additional factors include patient characteristics, bone penetration, and pharmacokinetics/pharmacodynamics. The use of non-traditional approaches to combat MDR, including the development of quorum sensing (QS)-targeted therapy, nanoparticle-based therapy, anti-virulence therapy, bacteriophage therapy, and antimicrobial peptides offer hope for future treatment strategies.

Multi-drug resistant Gram-positive bacteria

A study by Walls et al present 15 cases of methicillin resistant *Staphylococcus aureus* (MRSA). One third of patients were diagnosed with SSI and were successfully treated with antibiotics alone, either IV vancomycin or teicoplanin and PO linezolid. For those patients presenting with deep PJI, low rates of success were seen with attempted implant retention (1/5), often requiring staged revision followed by IV vancomycin then oral linezolid [54]. Cordero-Ampuero et al reported on 25 cases of late TKA PJI infected with methicillin-resistant *Staphylococci* (MRS), including MRSA and methicillin-resistant *coagulase-negative Staphylococci* (MR-CoNS). Infection was

eradicated in 22/25 (88%), predominantly using 2 stage revision + antibiotic cement (16/25). Antibiotic combinations were administered orally for 6 months to all patients, using one or more of the following agents; rifampin, ciprofloxacin, trimethoprim-sulphamethoxazole, fosfomycin, clindamycin, ofloxacin, linezolid or doxycycline. After 2nd stage reimplantation only IV prophylactic Cefazolin was administered for 5 days. An unsuccessful outcome (3/25) was observed in 2 patients managed with antibiotic treatment alone and in 1 patient after 2 stage revision [13]. A report by Jover Diaz et al on 24 cases of PJI and OM showed that linezolid is an effective, relatively safe, and well-tolerated alternative to glycopeptides for the treatment of osteoarticular infections caused by MRSA and MR-CoNS [25]. Bassetti et al 2014 found that linezolid is a potential option for multidrug-resistant *Staphylococci* and vancomycin-resistant *Enterococci* (VRE) for up to 4 weeks duration, with prolonged courses limited due to risk of drug-related toxicity [6]. Babis et al 2015 reported 31 cases of late THA PJI, including MRSA (11) and MRSE (10) infection. All patients were treated with 2 stage revision, antibiotic cement and postoperative antibiotics. Intravenous options for MR bacteria included a glycopeptide (vancomycin or teicoplanin) and trimethoprim-sulfamethoxazole or rifampicin. Oral antibiotic regimes consisted of ciprofloxacin and trimethoprim-sulfamethoxazole or rifampicin [5]. A retrospective study by Chang et al 2017 treated 16 cases of MRSA and MR-CoNS PJI with either debridement or 2-stage revision followed by IV daptomycin with success rates of 87.5%. The study emphasizes the need for careful monitoring of potential adverse effects during daptomycin treatment [12].

Multi-drug resistant Gram-negative bacteria

Ribera et al reported 15 PJI caused by MDR *Pseudomonas aeruginosa* and concluded that surgical treatment alongside combination therapy with *β*-lactams and colistin was significantly more effective than monotherapy alone. The results suggested potential synergism of colistin with b-lactams, especially against biofilm-associated infections with the additional advantage of allowing the dose of colistin to be reduced, reducing toxicity [42]. Frieler et at reported 27 cases of PJI TKA and THA. Infecting organisms included; MRSE, *Escherichia coli* (3MRGN), *Klebsiella pneumoniae* (3MRGN), *Enterococcus faecium* (VRE), MRSA, *Klebsiella oxytoca* (3MRGN), *Pseudomonas aeruginosa* (MRGN), *Enterobacter cloacae* complex (3MRGN), *Serratia marcescens* (3MRGN), *Proteus mirabilis* (3MRGN). Successful eradication was observed in 91% of cases following 2-stage revision and postoperative antibiotics. Antibiotic regimens for Gram-positive pathogens were vancomycin and meropenem and for Gram-negative pathogens; ceftazidim, colistin, or gentamicin [19]. Ferry et al used IV daptomycin, linezolid or tedizolid as long-term antibiotic suppression following arthroscopic local lysin DAIR for multi-drug resistant *Staphylococcus epidermidis* (MDRSE) [18]. Mancheño-Losa et al also showed good outcomes with a combination of colistin and *β*-lactams when managing BJI by MDR GNB. However, clinicians should be aware that colistin and fosfomycin have dosing challenges and may be associated with significant toxicity. [57]

Failure of Treatment:

Rudelli et al 2020 reported 57 cases of acute PJI of THA (31) and TKA (26) treated with DAIR, preoperative teicoplanin and amikacin followed by postoperative IV teicoplanin for 2 weeks and

4 weeks oral antibiotic. Treatment failure was observed in 55.6% of the Gram-negative MDR bacteria group, compared to 8.3% of the multidrug-sensitive bacteria group and 18.2% in MRSA group. They concluded that DAIR may not be effective in patients with rheumatoid arthritis and acute PJI caused by MDR bacteria [45]. A review by Perez-Jorge et al discussed the varying antibiotic options for PJI caused by MDR bacteria and concluded that individualized therapies should carefully consider the etiology, pathogenesis and antimicrobial susceptibility. Satisfactory clinical outcome could be further fostered by enhancing the multidisciplinary approach, with better collaboration in the antibiotic selection and the surgical management [38].

***In-vitro* studies:**

Many *in-vitro* studies showed promising results. A study by Pistella et al reporting 7 cases of device-associated infections (including PJI) showed that vancomycin or teicoplanin in combination with fosfomycin developed bactericidal synergism at a concentration of 1x MIC [40]. Littorin et al reported on 183 *Staphylococcus epidermidis* isolates from PJI cases and proposed that tedizolid may offer better tolerability and fewer adverse effects than linezolid. Consequently, it could be a potential treatment option for PJIs, either alone or in combination with rifampicin. [31]. Dusane et al found that vancomycin combined with bacterial efflux pump inhibitors was effective against intracellular *Staphylococcus aureus* [16]. Pfaller et al 2018 reported on an *in vitro* study of 1,252 isolates demonstrating sensitivity to dalbavancin. Isolates included *Staphylococcus aureus* (MRSA, MSSA), *coagulase-negative Staphylococci* (*S. epidermidis*, *S. lugdunensis*, Other CoNS), *Enterococcus faecalis*, *β-haemolytic Streptococci* (*S. agalactiae*, *S. dysgalactiae*, *S. pyogenes*), and viridans group *Streptococci* [39]. A narrative review by Berini et al highlights *in vitro* activity of nanoformulations of vancomycin, teicoplanin, and daptomycin against Gram-positive bacteria. It also includes promising findings from a limited number of animal studies and assessments of cellular toxicity [8]. A review of *in-vitro* studies by Khatoon et al focuses on quinoxaline derivatives as promising candidates to combat antimicrobial resistance. It showed quinoxaline had broad spectrum of activity against Gram-positive organisms (incl. MRSA), Gram-negative organisms (incl. *Acinetobacter calcoaceticus*), *Mycobacteria* (incl. *Mycobacterium tuberculosis*) and fungi (incl. *Candida* species) [28].

Summary:

The optimal antibiotic therapy for patients with PJI caused by resistant organisms remains inadequately addressed in the literature. Numerous antibiotic options are available. We provide a summary of the treatment options below:

- **Quinolone-resistant *Staphylococci*:** rifampicin combinations with clindamycin or linezolid. Daptomycin plus rifampicin (according to experimental studies and some reports)
- **Rifampin-resistant *Staphylococci*:** Monotherapy with linezolid, clindamycin or combinations of daptomycin alongside linezolid, fosfomycin or beta-lactams
- **MDR Gram-Negative Bacteria:** *β*-lactams with or without colistin or fosfomycin, or long-term *β*-lactam infusions.

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N.B. Reference 57 was published online in 2024; it was not in the extracted studies but was added for its importance as recommended by 2 delegates: Marisa del Lujan Sanchez and Joan Gómez-Junyent. It was agreed by all the team that it should be added.

Prisma