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QUESTION 9: What are the indications for utilizing fosfomycin, tigecycline and daptomycin, either instead of other antibiotics or in conjunction with other antibiotics, for the management of periprosthetic joint infections (PJIs)?

RECOMMDENATION FOR DAPTOMYCIN: Daptomycin is an alternative treatment for patients with PJIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

LEVEL OF EVIDENCE: Moderate

RECOMMENDATION FOR FOSFOMYCIN: Although there is no clinical experience using fosfomycin in PJIs, it could be considered in infections due to multi-drug resistant gram-positive (MDR-GP) or gram-negative bacteria (GNB) as a part of a combination regimen with daptomycin, rifampin or tigecycline when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

RECOMMENDATION FOR TIGEYCYLINE: Tigecycline could be considered for the treatment of MDR-GP or -GNB as a part of a combination regimen when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 4%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Daptomycin

Daptomycin is a cyclic lipopeptide with concentration-dependent bactericidal activity against gram-positive microorganisms. It is highly active against *Staphylococcus aureus*, coagulase-negative Staphylococci, *Enterococcus faecalis* and *Enterococcus faecium*, including both planktonic and biofilm-embedded bacteria [1]. Daptomycin combined with gentamicin has been shown to have synergistic activity on intracellular *S. aureus*. Additionally, daptomycin seems to exhibit activity against the stationary-phase bacteria inside a biofilm [2–4]. Several animal models of foreign-body infection demonstrated a high success rate with daptomycin but always in combination with rifampin [5,6].

Since its commercialization, several case series and one clinical trial have evaluated the efficacy of daptomycin in PJIs (Table 1). The first description [7] included 12 patients that received 4 mg/kg of daptomycin in monotherapy with a success rate of 45.5%. In addition, out of the five patients considered a success, only one retained the implant with oral suppressive therapy. Byren et al. [8] performed a

prospective, randomized controlled trial in PJIs treated with two-stage exchange to evaluate the safety and efficacy of 6 or 8 mg/kg of daptomycin in monotherapy for six weeks compared with the standard-of-care (vancomycin, teicoplanin or semisynthetic penicillin). A total of 75 patients were included and the clinical success rates were higher in daptomycin groups than in control group (58.3% for 6 mg/kg daptomycin vs. 60.9% for 8 mg/kg daptomycin vs. 38.1% for the comparators). The frequency of adverse events was similar in both groups; however, 16% and 22% of the patients in the 6 mg/kg and 8 mg/kg of daptomycin had increased creatine phosphokinase (CPK) levels (>500 U/L) vs. 8% in the control group.

In a retrospective study, Corona et al. [9] described 20 patients with PJI who received an average daptomycin dose of 6 mg/kg/day for a mean duration of 44.9 days. Fourteen patients were evaluated and four received rifampin (28.6%). The remission rate was higher than in previous studies (78.6%) and all patients treated with rifampin (including three acute PJI treated with debridement, antibiotic and implant retention (DAIR)) were in remission. Noteworthy, severe side effects occurred in two patients (10%) receiving daptomycin without rifampin and both required admission to the ICU. One developed a daptomycin-induced eosinophilic pneumonia and the other developed a massive rhabdomyolysis with acute renal failure. For this reason, authors recommended close monitoring for symptoms of myopathy with a weekly serial follow-up of serum creatinine. In addition, Jugun et al. [10] evaluated prospectively 16 patients with an osteoarticular infection treated with 8 mg/kg/day of daptomycin plus 600 mg of rifampin for a median duration of three weeks. Only six had a PJI but no clinically or laboratory-documented adverse events occurred that required adjustment or discontinuation of daptomycin therapy. All patients were in remission after an average of 15.8 (range 12.4-30) months of follow-up. Lora-Tamayo et al. [11] performed a retrospective, multi-centric study to evaluate the efficacy and safety of a 6-week course of daptomycin at 10 mg/kg plus rifampin in 20 patients with acute staphylococcal PJI managed with DAIR. Results were compared with 44 matched historical controls with PJI caused by fluoroquinolone-resistant staphylococci. The clinical failure rate was 50% in daptomycin group vs. 34% in historical controls (p = 0.265) and 29% and 30% had microbiological failure, respectively.

Malizos et al. [12] evaluated all patients with osteoarticular infection retrospectively collected from the European Cubicin® Outcomes Registry and Experience (EU-CORE) study that registered

TABLE 1. Summary of the clinical experience with daptomycin in PJIs including case series with more than five cases

Author, Year	Type of Study	Numberof Patients/ Type of PJI - Surgical Treatment	Dose, Duration	Rifampin (%)	Adverse Events Related with Daptomycin (%)	Follow-up Months (range)	MRSA n/Total (%)	Remission n/ Total Evaluated (%)
Rao 2006 [7]	P	12 / 5 early acute-DAIR 7 chronic-2S	4 mg/kg, 6 weeks	0	0	9 (range 7-13)	7/12 (58.3)	5/11 (45.5)
Byren 2012 [8]	RCT	75 / chronic-2S	6 mg/kg vs. 8 mg/kg vs. control, 6 weeks	0	CPK >500 u/L 6 mg/kg: 16% 8 mg/kg: 21.7% control: 8%	5-7	3/25 (12) 7/24 (30.4) 3/25 (12)	6 mg/kg: 14/24 (58) 8 mg/Kg:14/23 (61) control: 8/21 (38)
Corona 2012 [9]	R	20/ 8 early acute-5 DAIR and 3 2S 12 chronic-9 2S and 3 1S	6.6 mg/kg (median), 6.4 weeks	yes:8 (40)	CPK: 1 (12.5)	20 (range 12-41)	1/14 (7.1)	Acute infection: 5/6 (83.3) Chronic infection: 5/7 (71.4)
				no:12 (60)	CPK: 1 (8.3) Eosinophilic pneumonia: 1(8.3)			
Jugun 2013 [10]	P	16 osteoarticular infection (6 withPJI)	8.15 mg/kg (median) + rifampin 600 mg/d, 7.3 (range 2-17) weeks	16 (100)	0	15.8 (range 12.4-30)	3/6 (50)	totally or partially removed: 3/3 (100) DAIR: 3/3 (100)
Lora-Tamayo 2014 [11]	R	20 early acute-DAIR	10 mg/kg + rifampin 600 mg/d, 6 weeks	20 (100)	Rhabdomyolysis: 1 (5)	25 (range 24.4-32.3)	10/18 (55.5)	Daptomycin + Rifampin: 9/18 (50) Control group: 15/44 (34)
Chang 2017 [16]	R	16 / 5 early acute-DAIR 11 chronic-2S	8.3 mg/kg, 2 weeks	0	0	27	10/16 (62.5)	2S: 10/11 (91) DAIR: 4/5 (80)

P, prospective cohort; RCT, randomized control trial; R, retrospective cohort; PJI, prosthetic joint infection; MRSA, methicillin-resistant *S. aureus*; DAIR, debridement and implant retention; 2S, two-stage exchange; 1S, one-stage exchange.

real-world outcome data from patients receiving daptomycin. Out of 638 patients, 432 (67.7 %) had osteomyelitis and 206 (32.3%) had an orthopaedic device infection. More than 75% of the patients received ≥ 6 mg/kg of daptomycin during a median of 16 days (range, 1-176) for orthopaedic device infections. The remission rate was 81.8% overall and 85% in patients with PJI. Unfortunately, data about the type of infection (acute or chronic), methicillin-resistant *Staphylococcus aureus* (MRSA) rate and the surgical management was not reported. Overall, adverse events were reported in 78 (12.2%) patients, being severe in 39 (6.1%) and requiring discontinuation in 35 (5.5 %). The most recent report is a retrospective description of 16 patients treated with high doses of daptomycin (8.3 mg/kg per day) in monotherapy during a median of 14 days [13]. After this, all patients received oral antibiotics during a median of 35 days. The oral antibiotic combinations included were sulfamethoxazole/trimethoprim plus rifampin or fusidic acid plus rifampin. The study included 5 patients with an acute PJI treated with DAIR and 11 with a chronic PJI treated with two-stage exchange. It is important to highlight the high percentage of methicillin-resistant *S. aureus* (MRSA) (62.5%) and the high remission rate (87.5%). Specifically, there was one failure in acute PJIs (20%) and one among chronic ones (9%), both due to MRSA. No serious adverse events were reported.

In conclusion, a clinical trial showed that daptomycin at 6 or 8 mg/kg for six weeks had a higher cure rate than monotherapy with teicoplanin, vancomycin or a semi-synthetic penicillin. However, the clinical data suggest that ≥ 14 days of daptomycin in monotherapy is associated with adverse events (mainly CPK elevation). In contrast, other clinical studies combining daptomycin with rifampin did not observe problems with adverse events even after > 14 days of treatment and doses up to 10 mg/kg. This data suggests that rifampin could reduce the serum concentration of daptomycin (substrate of glycoprotein-P) but more data is necessary to support this hypothesis [13]. On the other hand, a short course of high dose (≥ 8 mg/kg) daptomycin without rifampin for the first two weeks of treatment followed by an oral rifampin combination seems to be well tolerated and associated with good outcome. Recent data show that the addition of daptomycin to cloxacillin or cefazolin may provide synergy, as shown by in vitro studies and animal experimental models [5,14]. This combination is promising to avoid the use of rifampin during the first 1-2 weeks of antibiotic treatment and to reduce the risk of selecting daptomycin-resistant mutants [15].

Fosfomycin

Fosfomycin has a broad-spectrum, including MDR-GP and (gram-negative (GN) microorganisms, a time-dependent bactericidal activity andis maintained in a low pH and in anaerobiosis [17–19]. Fosfomycin has a high bone penetration (bone:serum ratio of 43%), achieving concentrations above the minimum inhibitory concentration (MIC) for most susceptible bacteria [20]. There are three presentations: sodium fosfomycin for intravenous administration and trometamol and calcium salt for oral administration. Unfortunately, the oral bioavailability is < 20% for calcium salt and < 40% for trometamol. Therefore, only intravenous antibiotic is recommended for the treatment of bone infections [21].

Against GP, fosfomycin has demonstrated a potent in vitro synergistic activity against MRSA in combination with beta-lactams, daptomycin and linezolid. In addition, in an experimental foreign-body infection, fosfomycin combined with daptomycin or with rifampin were the second and the third regimens with the highest cure rate (defined as the percentage of eradication from the implant) only behind daptomycin plus rifampin and this was corroborated by other authors [22–26]. However, there is no clinical data supporting the efficacy of fosfomycin in PJI due to GP.

Fosfomycin has bactericidal activity in combination with carbapenems and colistin against carbapenemase-producing *Klebsiella pneumoniae* [27,28]. Corvec et al. [29] evaluated the activity of fosfomycin and tigecycline alone or in combination with other drugs against extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* strains in a foreign-body infection model. Fosfomycin was the only single agent for which the eradication of *E. coli* from cages was achieved and the combination that showed the highest antibiofilm activity was fosfomycin plus colistin, suggesting that fosfomycin should be considered in the treatment of MDR-GNB susceptible to fosfomycin strains. It is of note that fosfomycin could decrease the nephrotoxicity of aminoglycosides that in some occasions are the only active drug [30]. Although there is no clinical experience using fosfomycin in PJI due to GNB, it should be considered in infections due to MDR-GNB as a part of a combination regimen when the microorganism is susceptible.

Tigecycline

Tigecycline is active against GP and GN (except *Pseudomonas),* including vancomycin-resistant enterococci, MR-staphylococci, ESBL producing, carbapenemase (CP)-producing *Enterobacteriaceae* and *Acinetobacter* spp. Tigecycline has demonstrated synergistic activity against *Enterococcus* spp combined with rifampin and with amikacin or colistin against some MDR-*Enterobacteriaceae* spp, *Acinetobacter baumanii* or *Stenotrophomonas maltophilia* [31]. Data from foreign-body infection models due to MRSA showed that tigecycline in monotherapy was similar to vancomycinand in combination with rifampin was as effective as vancomycin with rifampin. Both options avoid the selection of rifampin-resistant mutants [32,33]. A recent study in healthy volunteers undergoing elective orthopaedic surgery demonstrated a good bone penetration after multiple doses of tigecycline (bone:serum ratio of 4) [34].

Clinical experience in osteomyelitis with tigecycline was documented in 13 cases with success in 85% but only one case was associated with an orthopaedic implant. In PJI the level of evidence is limited to a few case reports [35]. Vila et al.described three patients with early PJI of total hip arthroplasty due to MDR *A. baumannii* treated with debridement, implant retention and a high dose of tigecycline (100 mg every 12 hours) [36]. All patients received colistin concomitantly during a mean of 8.7 days and required at least one additional debridement, but all were asymptomatic after a median of 2.5 years. The major limitation for the prolonged use of tigecycline is the high frequency of nausea and vomiting. Vila et al. diluted tigecycline in 400 mL of dextrose and administered at a slow infusion rate in order to reduce the adverse events, and the therapy was well tolerated.

In contrast, de Sanctis evaluated three patients with a PJI due to carbapenem-resistant *K. pneumoniae* with poor outcomes [37]. All were polymicrobial infections, required multiple surgeries and complex antibiotic courses including tigecycline (two cases in monotherapy and one combined with amikacin first and with colistin later on). Prostheses were removed in two cases, but those patients died, and the one who survived required salvage limb amputation. In addition, resistant mutants to colistin and amikacin were selected while on antibiotic treatment however, the dose of tigecycline was not reported. Furthermore, Asseray et al. described four patients with PJI due to MDR- GP managed with implant removal and tigecycline during a median of 105 days (range 90-150) [38]. In addition, two patients received concomitant treatment with fosfomycin and one with linezolid. All patients but one (75%) were in remission after an average of 20.2 (range 14-32) months of follow-up. Only one patient treated with tigecycline plus fosfomycin experienced a moderate adverse event with anemia and thrombocytopenia, which was not

attributed with certainty to tigecycline; however, the dose of tigecycline was not specified. The rationale for increasing the dose (100 mg/12 hr) is based on its pharmacodynamic properties (area under the curve to minimum inhibitory concentration (AUC/MIC) ratio is the most predictive parameter related to clinical and microbiological efficacy), the presence of biofilms, and the multidrug-resistant profile of the involved organism [39]. Further experience and clinical studies are necessary, but tigecycline should be considered for the treatment of MDR-GP or GNB as a part of a combination regimen when the microorganism is susceptible.

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