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Ceftobripole: Experience in staphylococcal bacteremia

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ABSTRACT

Ceftobiprole is a new cephalosporin with an extended spectrum activity against the majority of microorganisms isolated in bacteremia including methicillin-susceptible (MSSA) and -resistant *S. aureus* (MRSA). This antibiotic has demonstrated a potent activity against MRSA in animal models of endocarditis in monotherapy but particularly in combination with daptomycin, suggesting that this combination could be a future option to improve the outcome of staphylococcal endovascular infections. In addition, the extended-spectrum ceftobiprole activity, including coagulase-negative staphylococci, *Enterococcus faecalis*, *Enterobacteriaceae* and *Pseudomonas aeruginosa* represents an advantage for use as empirical therapy in bacteremia potentially caused by a broad spectrum of microorganisms, such as in catheter-related bacteremia.

INTRODUCTION

Staphylococcus aureus is one of the leading causes of bloodstream infections [1] and in the recent years the most common microorganism causing endocarditis [2]. Despite therapeutic advances, a recent study on 3395 consecutive adult patients with *S. aureus* bacteremia (SAB) from 20 care centers in Europe and the United States reported a crude 14 and 90-day mortality rate of 14.6% and 29.2%, respectively [3]. Source control (catheter removal, abscess drainage) and early administration of an adequate antibiotic treatment are factors independently associated with success [4], however, randomized control trials to determine the best antibiotic treatment in SAB are scarce and new data mainly arise from observational studies. The major advances can be summarized as follows:

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1) The *in vitro* synergy between beta-lactams and aminoglycosides has not been translated into a clinical benefit probably due to the unacceptable risk of nephrotoxicity [5] and it is no longer recommended [6].

2) Vancomycin is associated with a higher failure rate than beta-lactams against methicillin-susceptible *S. aureus* (MSSA), even when vancomycin is given empirically and switched to a beta-lactam within 72h after the first blood culture [7].

3) For the treatment of methicillin-resistant *S. aureus* (MRSA) bacteremia, vancomycin should be dosed to achieve an AUC/MIC≥400. To obtain this goal, a minimum serum concentration of 15-20 mg/L is necessary, and the recommended dose is 15-20 mg/kg/12h. In critically ill patients, a loading dose of 30-35 mg/kg is suggested to early achieve the pharmacodynamic goal [8].

4) Vancomycin MIC of 2 mg/L has been associated with a higher mortality rate in MRSA bacteremia probably due to the low probability to attain the pharmacodynamic target [9, 10], and the higher prevalence of hetero-resistance to vancomycin in those strains with a MIC≥2 mg/L [11].

5) The therapeutic range of vancomycin (serum concentration between 15 and 20 mg/L) overlaps with the nephrotoxic range [12].

6) A randomized clinical trial in *S. aureus* bacteremia comparing daptomycin vs. anti-staphylococcal penicillin (for MSSA) or vancomycin (for MRSA) plus gentamicin for the first 4 days showed that daptomycin is a suitable alternative but still associated with a high failure rate for high-inoculum infections like left-sided endocarditis because of a risk of selecting strains with reduced susceptibility [13]. In addition, a loss of daptomycin susceptibility in the absence of any administered antibiotic has been recently observed in an experimental model of prosthetic joint infection, probably as a result of *in vivo* selection pressure from cationic host peptides [14, 15].

In the last guidelines from the Infectious Diseases Society of America (IDSA) [6], vancomycin is still the first line choice

but daptomycin is considered an alternative. Recent recommendations from Spanish experts support the use of high dose daptomycin (8-10 mg/kg/24h), and for high-inoculum infections, combination therapy with a second active antibiotic [16, 17]. These findings clearly point out 1) the need of alternative treatments for *S. aureus* bacteremia and 2) the major efficacy issues of beta-lactams over any alternative.

Table 1 **Cure rate at test of cure and 30-day mortality of patients with bacteremia in the 4 pivotal studies of ceftobiprole and comparators.**

Outcome	Ceftobiprole, n/N (%)	Comparator, n/N (%)
Clinical cure rate at test of cure		
Any staphylococcal bacteremia	22/45 (48.9)	22/50 (44)
Coagulase-negative staphylococci	10/22 (45.5)	10/22 (45.5)
S. aureus	12/23 (52.2)	12/28 (42.9)
MSSA	4/9 (44.4)	7/15 (46.7)
MRSA	5/9 (55.6)	2/9 (22.2)
30-day all cause mortality		
Any staphylococcal bacteremia	4/45 (8.9)	8/50 (16)
Coagulase-negative staphylococci	1/22 (4.5)	2/22 (9.1)
S. aureus	3/23 (13)	6/28 (21.4)
MSSA	1/9 (11.1)	2/15 (13.3)
MRSA	0/9	2/9 (22.2)

ACTIVITY OF CEFTOBIPROLE AGAINST STAPHYLOCOCCI

Ceftobiprole medocaril is a new cephalosporin with *in vitro* activity against *S. aureus* and coagulase-negative staphylococci (CoNS). In a recent study, 99.5% of 15.426 *S. aureus* isolates were susceptible to ceftobiprole at the EUCAST breakpoint of 2 mg/L. The minimum inhibitory concentrations of 90% (MIC_{90}) for methicillin susceptible and resistant isolates were 0.5 and 2 mg/L, respectively. Against CoNS, the ceftobiprole MIC_{90} was 0.25 and 2 mg/L against methicillin susceptible and -resistant isolates, respectively [18]. Ceftobiprole's activity was not affected by vancomycin MIC and it remained active against isolates with an elevated vancomycin MIC (2 mg/L). Ceftobiprole has a time-dependent bactericidal activity that is optimal at 2 to 8 times the MIC [19]. In the rabbit endocarditis model using MRSA strains with a MIC of 2 mg/L, ceftobiprole was as effective as vancomycin [20, 21] and even superior to vancomycin, daptomycin and linezolid using the same model but a different strain with a ceftobiprole MIC of 4 mg/L [22]. In a rat model of endocarditis the efficacy of a continuous infusion of ceftobiprole to maintain serum concentrations about 6, 12 or 25 mg/L was evaluated [23]. The highest concentration sterilized 100% of the vegetations and the other two >90%, supporting the *in vitro* pharmacodynamic models showing a bactericidal activity against MRSA when T>MIC is 100% [24]. In these animal models, no selection of ceftobiprole resistant strains was detected in line with *in vitro* data showing very low frequency of resistance development after single-passage selection [19]. These studies also demonstrated a high stability of ceftobiprole, after 24h exposure to a high inoculum (10^9 CFU) of a penicillinase-producing *S. aureus* strain, being even more stable than methicillin. This is of interest since a high failure rate in high inoculum infections (endocarditis) has been observed with cephalosporins like cefazolin when the causative strain is producing type A beta-lactamase [25]. The activity of ceftobiprole against type A, B, and C beta-lactamase producing MSSA has been tested and a slight increase in the MIC was documented when comparing standard and high inoculum of type A, B and C producing MSSA beta-lactamase positive strains but the MIC remained ≤2 mg/L in all cases [26].

CLINICAL EXPERIENCE WITH CEFTOBIPROLE IN BACTERAEMIC PATIENTS

The clinical experience is scarce but there were bacteraemic patients within the 4 pivotal phase 3 clinical trials comparing ceftobiprole with other alternatives for community (CAP), hospital (HAP) acquired pneumonia, and for complicated skin and soft tissue infections (cSSTI) [27-30]. A pooled analysis of these 4 trials assessed the efficacy of ceftobiprole and comparators against staphylococcal bacteraemia in cSSTI, CAP, and HAP. Comparators included vancomycin (cSSTI), vancomycin plus ceftadizime (cSSTI), ceftriaxone (with linezolid in cases of suspected MRSA) (CAP) and ceftazidime plus linezolid (HAP) (Rello J, Rahav, Scheeren T, Saulay M, Engelhardt M, Welte T. Pooled analysis of clinical cure and mortality with ceftobiprole medocaril versus comparators in staphylococcal bacteremia in complicated skin infections, community- and hospital-acquired pneumonia. ECCMID 2016: O-318). The outcomes showed that clinical responses were similar with ceftobiprole and standard-of-care comparators (table 1). In patients with MRSA, there was a trend towards improved clinical cure rates at test of cure (55.6% vs. 22.2%) and all-cause mortality at day 30 (0 vs. 22.2%) with ceftobiprole compared with other regimens (table 1). A double-blind, randomised, non-inferiority study to compare ceftobiprole (500 mg/8h) and daptomycin (6 mg/kg/24h) in adult patients with *S. aureus* bacteraemia, including right-sided infective endocarditis, is ongoing (https://clinicaltrials.gov/ct2/show/NCT03138733).

The high mortality associated with particular pathologies such as endovascular infections deserves a particular attention since several *in vitro* antibiotic combinations have shown synergism but clinical trials to test these new therapeutic alternatives are scarce [3]. For instance, beta-lactams have shown *in vitro* synergy with vancomycin against MRSA [31-34] and a subsequent clinical trial randomized 60 patients with MRSA bacteremia to receive vancomycin alone or in combination with flucloxacillin for 7 days [35]. The mean time to resolution of bacteremia in the combination group was 1.94 days compared with 3 days in the vancomycin group (P = 0.06). In line with this, ceftobiprole has also demonstrated *in vitro* synergism with vancomycin and in a rat model

of endocarditis, the combination of sub-therapeutic dose of ceftobiprole and vancomycin was as effective as monotherapy with standard ceftobiprole dose against MRSA and VISA strains [36, 37]. However, the combination with vancomycin does not avoid the potential risk of nephrotoxicity, therefore, other alternatives are required. The most promising approach is the association of daptomycin with a beta-lactam since 1) the *in vitro* synergy has been described [38-41], 2) the ability of beta-lactams to avoid the selection of daptomycin resistant mutants, 3) the dual effect of beta-lactams, potentiating the activity of cationic host peptides against MSSA and MRSA [42], and 4) two retrospective case series exist showing good clinical results [43, 44]. Sub-inhibitory concentrations of ceftobiprole reduced daptomycin MICs >4-fold which was confirmed in time-kill studies [45]. Interestingly, a recent case report of a patient with a prosthetic valve endocarditis due to MRSA; who failed on daptomycin monotherapy and to daptomycin plus piperacillin-tazobactam, was switched to daptomycin plus ceftobiprole due to persistent bacteremia and fever. After 48h, under the new combination, the patient became afebrile and he was operated with good outcome afterwards [46].

A potential concern is the adequate dose of ceftobiprole for bacteremia and endocarditis. The pharmacodynamic target derived from skin and soft tissue infections is a free concentration over the MIC for 50% of the interval between 2 consecutive doses (>50% *f*T>MIC). The probability of achieving this target, with the current approved dose (500 mg/8h in 2h infusion), is >90% for MIC≤4 mg/L [47]. However, a higher exposure (100% *f*T>MIC) is associated with a potent bactericidal activity [24] and it would be the preferred target for severe and high inoculum infections. Using the current dose, the probability of obtaining a 100% of *f*T>MIC for MRSA strains is lower but it can be significantly improved by giving 500 mg/6h or 1 g/8h both infused in 4h or any dose in continuous infusion. A recent open-label study carried out in 33 adults treated in the ICU examined the pharmacokinetics of high-dose ceftobiprole administered over a longer infusion period (1000 mg over 4 h/12h for patients with a CrCl 50-79 mL/min and /8h for CrCl≥80 mL/min) for 1 day [48]. Ceftobiprole was well tolerated and a 100% of *f*T>MIC of 4 mg/L was obtained regardless of the CrCl.

On the other hand, catheters are the leading cause of nosocomial bacteremia and according to recent experience; although Gram-positives are still the most frequent microorganisms, Gram-negative pathogens including *Enterobacteriaceae* and *P. aeruginosa* are significantly increasing [49, 50]. The extended-spectrum activity, including methicillin-resistant coagulase-negative staphylococci, *Enterococcus faecalis* and Gram-negatives including *P. aeruginosa,* of ceftobiprole is an advantage for a monotherapy as empirical treatment for catheter related bacteremia.

In conclusion, ceftobiprole is a new anti-MRSA beta-lactam with a time-dependent bactericidal activity and strong data in animal models of endocarditis showing that this monotherapy is more effective than vancomycin and that the combination with daptomycin has a potent synergistic activity. Therefore, ceftobiprole should be considered as a potential empirical option when MRSA bacteremia is suspected and in combination with daptomycin for the treatment of endovascular infections as a primary option or as a salvage therapy. In the future, it is necessary to collect more clinical experience with this antibiotic and to evaluate the most adequate dosage particularly for more severe infections.

REFERENCES

1. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. Clin Microbiol Infect 2013; 19:492–500. doi: 10.1111/1469-0691.12144
2. Fowler VG, Justice A, Moore C, et al. Risk factors for hematogenous complications of intravascular catheter-associated *Staphylococcus aureus* bacteremia. Clin Infect Dis 2005; 40:695–703. doi: 10.1086/427806
3. Kaasch AJ, Barlow G, Edgeworth JD, et al. *Staphylococcus aureus* bloodstream infection: A pooled analysis of five prospective, observational studies. J Infect. 2014;68(3):242-51. doi: 10.1016/j.jinf.2013.10.015.
4. Paul M, Kariv G, Goldberg E, et al. Importance of appropriate empirical antibiotic therapy for methicillin-resistant *Staphylococcus aureus* bacteraemia. J Antimicrob Chemother 2010; 65:2658–2665. doi: 10.1093/jac/dkq373.
5. Korzeniowski O, Sande MA. Combination antimicrobial therapy for *Staphylococcus aureus* endocarditis in patients addicted to parenteral drugs and in nonaddicts: A prospective study. Ann Intern Med 1982; 97:496–503. doi : 10.7326/0003-4819-97-4-496
6. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011; 52:e18–55. doi: 10.1093/cid/ciq146
7. McConeghy KW, Bleasdale SC, Rodvold KA. The Empirical Combination of Vancomycin and a β-Lactam for Staphylococcal Bacteremia. Clin Infect Dis 2013; 57:1760–1765. doi: 10.1093/cid/cit560
8. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health-Syst Pharm 2009; 66:82–98. doi: 10.2146/ajhp080434
9. Soriano A, Marco F, Martínez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis 2008; 46:193–200. doi: 10.1086/524667
10. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of Vancomycin Exposure on Outcomes in Patients with Methicillin-Resistant Staphylococcus aureus Bacteremia: Support for Consensus Guidelines Suggested Targets. Clin Infect Dis 2011; 52:975–981. doi: 10.1093/cid/cir124.
11. Musta AC, Riederer K, Shemes S, et al. Vancomycin MIC plus het-

eroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: trends over 11 years. J Clin Microbiol 2009; 47:1640–1644. doi: 10.1128/JCM.02135-08

12. Bosso JA, Nappi J, Rudisill C, et al. Relationship between Vancomycin Trough Concentrations and Nephrotoxicity: a Prospective Multicenter Trial. Antimicrob Agents Chemother 2011; 55:5475–5479. doi: 10.1128/AAC.00168-11.
13. Fowler VG, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006; 355:653–665. doi: 10.1056/NEJMoa053783
14. Mishra NN, Bayer AS, Moise PA, Yeaman MR, Sakoulas G. Reduced susceptibility to host-defense cationic peptides and daptomycin coemerge in methicillin-resistant from daptomycin-naive bacteremic patients. J Infect Dis 2012; 206:1160–1167. doi: 10.1093/infdis/jis482
15. Mishra NN, Yang S-J, Chen L, et al. Emergence of Daptomycin Resistance in Daptomycin-Naïve Rabbits with Methicillin-Resistant *Staphylococcus aureus* Prosthetic Joint Infection Is Associated with Resistance to Host Defense Cationic Peptides and mprF Polymorphisms. PLoS ONE 2013; 8:e71151. doi: 10.1371/journal.pone.0071151
16. Mensa J, Soriano A, Llinares P, et al. [Guidelines for antimicrobial treatment of the infection by *Staphylococcus aureus*]. Rev Esp Quimioter. 2013; 26 Suppl 1:1–84. PMID: 23824510
17. Gudiol F, Aguado JM, Pascual A, et al. [Consensus document for the treatment of bacteremia and endocarditis caused by methicillin-resistent *Staphylococcus aureus*. Enferm Infecc Microbiol Clin. 2009;27(2):105-15. doi: 10.1016/j.eimc.2008.09.003
18. Farrell DJ, Flamm RK, Sader HS, Jones RN. Ceftobiprole Activity against over 60,000 Clinical Bacterial Pathogens Isolated in Europe, Turkey, and Israel from 2005 to 2010. Antimicrob Agents Chemother 2014; 58:3882–3888. doi: 10.1128/AAC.02465-14
19. Bogdanovich T, Ednie LM, Shapiro S, Appelbaum PC. Antistaphylococcal activity of ceftobiprole, a new broad-spectrum cephalosporin. Antimicrob Agents Chemother 2005; 49:4210–4219. doi: 10.1128/AAC.49.10.4210-4219.2005
20. Fung-Tomc JC, Clark J, Minassian B, et al. In vitro and in vivo activities of a novel cephalosporin, BMS-247243, against methicillin-resistant and -susceptible staphylococci. Antimicrob Agents Chemother 2002; 46:971–976. doi: 10.1128/aac.46.4.971-976.2002
21. Chambers HF. Evaluation of ceftobiprole in a rabbit model of aortic valve endocarditis due to methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus*. Antimicrob Agents Chemother 2005; 49:884–888. doi: 10.1128/AAC.49.3.884-888.2005
22. Tattevin P, Basuino L, Bauer D, Diep BA, Chambers HF. Ceftobiprole is superior to vancomycin, daptomycin, and linezolid for treatment of experimental endocarditis in rabbits caused by methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2010; 54:610–613. doi: 10.1128/AAC.00886-09
23. Entenza JM, Hohl P, Heinze-Krauss I, Glauser MP, Moreillon P. BAL9141, a novel extended-spectrum cephalosporin active against methicillin-resistant *Staphylococcus aureus i*n treatment of experimental endocarditis. Antimicrob Agents Chemother 2002; 46:171–177. doi: 10.1128/aac.46.1.171-177.2002
24. Zhanel GG, Voth D, Nichol K, Karlowsky JA, Noreddin AM, Hoban DJ. Pharmacodynamic activity of ceftobiprole compared with vancomycin versus methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate Staphylococcus aureus (VISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) using an in vitro model. J Antimicrob Chemother 2009; 64:364–369. doi: 10.1093/jac/dkp176.
25. Nannini EC, Singh KV, Murray BE. Relapse of type A beta-lactamase-producing *Staphylococcus aureu*s native valve endocarditis during cefazolin therapy: revisiting the issue. Clin Infect Dis 2003; 37:1194–1198. doi: 10.1086/379021
26. Nannini EC, Stryjewski ME, Singh KV, et al. Determination of an inoculum effect with various cephalosporins among clinical isolates of methicillin-susceptible *Staphylococcus aureus*. Antimicrob Agents Chemother 2010; 54:2206–2208. doi: 10.1128/AAC.01325-09
27. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin Infect Dis 2008; 46:647–655. doi: 10.1086/526527.
28. Nicholson SC, Welte T, File TM, et al. A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. Int J Antimicrob Agents 2012; 39:240–246. doi: 10.1016/j.ijantimicag.2011.11.005
29. Awad SS, Rodriguez AH, Chuang YC, et al. A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia. Clin Infect Dis 2014; 59:51–61. doi: 10.1093/cid/ciu219
30. Noel GJ, Strauss RS, Amsler K, Heep M, Pypstra R, Solomkin JS. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. Antimicrob Agents Chemother 2008; 52:37–44. doi: 10.1128/AAC.00551-07
31. Domenech A, Ribes S, Cabellos C, et al. A mouse peritonitis model for the study of glycopeptide efficacy in GISA infections. Microb Drug Resist 2005; 10:346–353.
32. Domaracki BE, Evans AM, Venezia RA. Vancomycin and oxacillin synergy for methicillin-resistant staphylococci. Antimicrob Agents Chemother 2000; 44:1394–1396. doi: 10.1089/mdr.2004.10.346
33. Drago L, De Vecchi E, Nicola L, Gismondo MR. In vitro evaluation of antibiotics' combinations for empirical therapy of suspected methicillin resistant *Staphylococcus aureus* severe respiratory infections. BMC Infect Dis 2007; 7:219. doi: 10.1186/1471-2334-7-111
34. Hagihara M, Wiskirchen DE, Kuti JL, Nicolau DP. In vitro pharmacodynamics of vancomycin and cefazolin alone and in combination against methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2012; 56:202–207. doi: 10.1128/AAC.05473-11.
35. Davis JS, O'Sullivan MVN, Robinson JO, et al. Combination of Van-

comycin and β-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial. Clin Infect Dis 2016; 62:173–180. doi: 10.1093/cid/civ808.

36. Fernandez J, Abbanat D, Shang W, et al. Synergistic activity of ceftobiprole and vancomycin in a rat model of infective endocarditis caused by methicillin-resistant and glycopeptide-intermediate *Staphylococcus aureus*. Antimicrob Agents Chemother 2012; 56:1476–1484. doi: 10.1128/AAC.06057-11
37. Entenza JM, Veloso TR, Vouillamoz J, Giddey M, Majcherczyk P, Moreillon P. In vivo synergism of ceftobiprole and vancomycin against experimental endocarditis due to vancomycin-intermediate *Staphylococcus aureus*. Antimicrob Agents Chemother 2011; 55:3977–3984. doi: 10.1128/AAC.00402-11
38. Rand KH, Houck HJ. Synergy of daptomycin with oxacillin and other beta-lactams against methicillin-resistant S*taphylococcus aureus*. Antimicrob Agents Chemother 2004; 48:2871–2875. doi: 10.1128/AAC.48.8.2871-2875.2004
39. Yang S-J, Xiong YQ, Boyle-Vavra S, Daum R, Jones T, Bayer AS. Daptomycin-oxacillin combinations in treatment of experimental endocarditis caused by daptomycin-nonsusceptible strains of methicillin-resistant *Staphylococcus aureus* with evolving oxacillin susceptibility (the 'seesaw effect'). Antimicrob Agents Chemother 2010; 54:3161–3169. doi: 10.1128/AAC.00487-10
40. Steed ME, Vidaillac C, Rybak MJ. Novel daptomycin combinations against daptomycin-nonsusceptible methicillin-resistant *Staphylococcus aureus* in an in vitro model of simulated endocardial vegetations. Antimicrob Agents Chemother 2010; 54:5187–5192. doi: 10.1128/AAC.00536-10
41. Komatsuzawa H, Suzuki J, Sugai M, Miyake Y, Suginaka H. Effect of combination of oxacillin and non-beta-lactam antibiotics on methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 1994; 33:1155–1163. doi: 10.1093/jac/33.6.1155
42. Yeaman MR, Norman DC, Bayer AS. Platelet microbicidal protein enhances antibiotic-induced killing of and postantibiotic effect in S*taphylococcus aureus*. Antimicrob Agents Chemother 1992; 36:1665–1670. doi: 10.1128/aac.36.8.1665
43. Dhand A, Bayer AS, Pogliano J, et al. Use of antistaphylococcal beta-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant Staphylococcus aureus: role of enhanced daptomycin binding. Clin Infect Dis 2011; 53:158–163. doi: 10.1093/cid/cir340.
44. Moise PA, Amodio Groton M, Rashid M, et al. Multicenter Evaluation of the Clinical Outcomes of Daptomycin with and without Concomitant -Lactams in Patients with *Staphylococcus aureu*s Bacteremia and Mild to Moderate Renal Impairment. Antimicrob Agents Chemother 2013; 57:1192–1200. doi: 10.1128/AAC.02192-12
45. Barber KE, Werth BJ, Ireland CE, et al. Potent synergy of ceftobiprole plus daptomycin against multiple strains of *Staphylococcus aureus* with various resistance phenotypes. J Antimicrob Chemother 2014; 69:3006–3010. doi: 10.1093/jac/dku236.
46. Oltolini C, Castiglioni B, Tassan Din C, et al. Meticillin-resistant *Staphylococcus aureus* endocarditis: first report of daptomycin plus ceftobiprole combination as salvage therapy. Int J Antimicrob Agents 2016; 47:502–504. doi: 10.1016/j.ijantimicag.2016.04.006.
47. Kimko H, Xu X, Nandy P, et al. Pharmacodynamic profiling of ceftobiprole for treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother 2009; 53:3371–3374. doi: 10.1128/AAC.01653-08
48. Torres A, Mouton JW, Pea F. Pharmacokinetics and Dosing of Ceftobiprole Medocaril for the Treatment of Hospital- and Community-Acquired Pneumonia in Different Patient Populations. Clin Pharmacokinet 2016; 55:1507–1520. doi: 10.1007/s40262-016-0418-z
49. Marcos M, Soriano A, Iñurrieta A, et al. Changing epidemiology of central venous catheter-related bloodstream infections: increasing prevalence of Gram-negative pathogens. J Antimicrob Chemother 2011; 66:2119–2125. doi: 10.1093/jac/dkr231
50. Ripa M, Morata L, Rodríguez-Núñez O, et al. Short-Term Peripheral Venous Catheter-Related Bloodstream Infections: Evidence for Increasing Prevalence of Gram-Negative Microorganisms from a 25-Year Prospective Observational Study. Antimicrob Agents Chemother 2018; 62(11). pii: e00892-18. doi: 10.1128/AAC.00892-18