Intensive Care Med
DOI 10.1007/s00134-016-4572-4

EDITORIAL

Treatment of severe MRSA infections: current practice and further development

José-Artur Paiva[1*] and Philippe Eggimann[2]

Staphylococcus aureus is one of the "ESKAPE pathogens", considered to require urgent development of new therapies, in spite of some decline in the incidence of methicillin-resistant *S. aureus* (MRSA) infections. Vancomycin, a glycopeptide with an excellent spectrum of activity against Gram-positive pathogens through inhibition of cell wall synthesis, has been the mainstay of treatment for MRSA. However, MRSA infections are associated with increased morbidity and mortality, when compared with methicillin-sensitive *S. aureus* (MSSA), and several weaknesses have been identified related to vancomycin use, namely slower bacterial killing than oxacillin, poor penetration in the lungs and central nervous system, and frequent underdosage in critically ill patients as a result of increased volume of distribution and renal hyperfiltration [1].

Four main strategies may be used to circumvent the problems related with vancomycin use.

One is the use of individualized dosing of vancomycin to reach the PK/PD target of AUC/MIC $\geq$ 400 that seems to improve clinical outcome [1], both in pneumonia and bacteremia. According to the 2009 Infectious Diseases Society of America (IDSA) vancomycin therapeutic guidelines [2], a loading dose of 25–30 mg/kg actual body weight should be used, followed by 15–20 mg/kg q8–12 h. Vancomycin serum levels and vancomycin MRSA MIC by Etest must be measured routinely. Trough levels between 15 and 20 μg/mL are recommended [2], but the probability of target attainment is unlikely in high vancomycin MIC infections, and MIC values above 1 μg/mL significantly predict treatment failure and mortality [3]. Although these outcomes may not reflect antibiotic failure per se but may rather be a marker of specific pathogen virulence characteristic, as a similar association between high vancomycin MIC and outcomes was reported in MSSA infections treated with flucloxacillin [4], it seems wise to aim at higher vancomycin levels in the case of MRSA MIC > 1 μg/mL. However, these higher doses are associated with increased incidence of nephrotoxicity. Continuous infusion has been associated with lower rates of nephrotoxicity (nephrotoxicity threshold around 28 μg/mL), higher steady state concentration, faster achievement of target concentrations, less variability in serum concentrations, and simpler AUC assessment, compared with intermittent dosing [5]; however, there is no evidence of higher effectiveness of the continuous regimen [6].

Another proposed strategy is the use of more recently developed antibiotics with activity against MRSA. Globally, no drug has shown superiority to vancomycin in the treatment of MRSA infections with the possible exception of linezolid in hospital-acquired pneumonia (HAP). A multicenter randomized controlled trial (RCT) comparing vancomycin to linezolid in the treatment of MRSA HAP [7] showed that both clinical and microbiological cure rates were significantly higher in the linezolid arm compared with vancomycin, but 60-day mortality was similar in both arms. A recent meta-analysis included data from the above trial and observed similar efficacies for linezolid and vancomycin, including in microbiologically proven MRSA pneumonia [8]. The lipopeptide daptomycin, which is inactivated by pulmonary surfactant, is currently the only antibiotic to have shown noninferiority to vancomycin in the treatment of MRSA bacteremia and even a possible superiority in infections caused by MRSA with high vancomycin MIC [9]. Dosages of 8–10 mg/kg/day should be used for complicated bacteremia and, preferably, in combination with other agents [10], both to improve outcomes and to decrease the emergence of resistance,

*Correspondence: jarturpaiva@gmail.com
[1] Department of Emergency and Intensive Care, Faculty of Medicine, Grupo de Infecçao e Sepsis, Centro Hospitalar Sao Joao, University of Porto, Porto, Portugal
Full author information is available at the end of the article

Table 1 Dose, PK/PD dose adaptations, and drug interactions of the main anti-MRSA drugs in the critically ill patient

Antibiotic	Dose	Dose adaptation in renal failure	PK/PD issues	Drug interactions
Vancomycin	25–30 mg/kg IV loading dose, followed by 15–20 mg/kg q8–12 h IV	Dosing adjustments are needed; trough serum concentrations monitoring recommended aiming at 15–20 μg/mL; use of alternative drugs may be preferable If CVVHF: 30 mg/kg loading dose and 20 mg/kg q8–12 h	"Slow" bactericidal activity; AUC/MIC drug; difficult penetration into lung and CNS; 40 mg/kg/day by continuous infusion after loading dose, with monitoring of serum concentrations aiming at 20–25 μg/mL is probably preferable for treatment of MRSA with vancomycin MIC >1 (less nephrotoxicity and easier dose management)	Increases serum concentration of vecuronium; addition of aminoglycoside or rifampin did not prove to be synergistic; evidence of synergy between beta-lactams and vancomycin; maybe, vancomycin + flucloxacillin for difficult-to-treat infections
Linezolid	600 mg q12 h IV or PO	No dose adaptation in renal failure; in CVVHF: 600 mg q8 h IV	Bacteriostatic; 100 % bioavailable oral formulation; low serum concentrations; good penetration into lung and SST; AUC/MIC and T > MIC drug; higher cure rates but similar mortality to vancomycin in HAP/VAP; continuous infusion may be preferable in the obese patient	Increases serum concentration of SSRI; addition of aminoglycoside or rifampin did not prove to be synergistic
Daptomycin	8–10 mg/kg q24 h IV for bacteremia and 6–8 mg/kg q24 h IV for SSTI	If Cr Cl < 30 mL/min, same dose q48 h In CVVHF: 8–10 mg/kg q24 h IV for bacteremia and 6–8 mg/kg q24 h IV for SSTI	Bactericidal; concentration-dependent antibiotic; good serum concentrations; inactivated by pulmonary surfactant (not for pneumonia); possibly superior to vancomycin in bacteremia caused by MRSA with high vancomycin MIC	Addition of aminoglycoside or rifampin did not prove to be synergistic; evidence of synergy between beta-lactams and vancomycin; maybe, vancomycin + flucloxacillin for difficult-to-treat infections; combination may improve outcome and decrease emergence of resistance
Tigecycline	100 mg IV loading dose, followed by 50 mg q12 h IV	No dose adaptation in renal failure In CVVHF: 150 mg loading dose, followed by 100 mg q12	Bacteriostatic; AUC/MIC drug; high protein binding; in difficult-to-treat infections and in pneumonia, 100 mg q12 h IV after a loading dose of 150 mg should be used owing to low serum and lung concentrations with traditional dosing	Increases serum concentration of warfarin; use as monotherapy should be avoided
Ceftaroline	600 mg q12 h IV	If Cr Cl 31–50 mL/min: 400 mg q12 h; if Cr Cl 15–30 mL/min: 300 mg q12 h; if Cr Cl < 15 mL/min: 200 mg q12 h	Bactericidal; time-dependent drug; high concentrations in lung and SST	

AUC area under the curve, *CNS* central nervous system, *Cr Cl* creatinine clearance, *CVVHF* continuous venovenous hemofiltration, *HAP* hospital-acquired pneumonia, *MIC* minimal inhibitory concentration, *SSRI* selective serotonin reuptake inhibitors, *SST* skin and soft tissue, *SSTI* skin and soft tissue infection, *VAP* ventilator-associated pneumonia

which has been described mainly associated with prior exposure to vancomycin and retained prosthetic devices. The development of ceftaroline and ceftobiprole, cephalosporins with in vitro activity against MRSA owing to their affinity for the penicillin-binding protein PBP2a, offers great promise in the treatment of MRSA, as β-lactams are associated with improved clinical outcomes when compared with glycopeptides for the treatment of MSSA infections [11]. These agents should be restricted to the treatment of MRSA infections, as it is likely that usage will be associated with increased rates of resistance that have already been observed. Tigecycline, a glycylcycline highly active against MRSA in vitro, cannot be recommended as first-line therapy in serious MRSA infections, as there is insufficient data available and reports exist of higher mortality and lower cure probably due to PK/PD considerations including high protein biding, inadequate AUC/MIC with standard dosing, low serum concentrations, and poor penetration into some tissues [12]. However, it may be useful, in combination regimens, namely for skin and soft tissue or intra-abdominal infections [13]. Oritavancin, dalbavancin, and telavancin are semisynthetic lipopolypeptide analogues of vancomycin. All three show activity against MRSA and vancomycin-intermediate *S. aureus* (VISA) and oritavancin also against vancomycin-resistant *S. aureus* (VRSA). The long half-lives and complex PK of the first two make them unsuitable for critically ill patients unless other options do not exist [12].

Thirdly, combination therapy may be used. Combinations of two primary active agents (such as vancomycin plus linezolid) or the addition of gentamicin or rifampin to either vancomycin or daptomycin did not prove to be synergistic [6]. Rifampin, owing to its activity in biofilms, may retain a role as a secondary agent in prosthetic valve endocarditis and bone/joint infections with or without infected implants, but should only be started after clearance of bacteremia. Gentamicin's role is restricted to native valve endocarditis or as an adjunctive agent to daptomycin in bacteremia non-responsive to vancomycin. Cotrimoxazole may represent a potent alternative to all existing anti-staphylococcal agents provided that in vitro activity is demonstrated [6]. Although MRSA is inherently resistant to nearly all β-lactam antibiotics, this class of drugs has consistently shown evidence of synergy with either vancomycin or daptomycin in multiple in vitro studies and in a small number of observational studies. The mechanism may include β-lactam-induced potentiation of host defense peptide activity against *S. aureus*, β-lactam-induced alteration of MRSA cell wall which allows for improved vancomycin binding, or a "see-saw" effect whereby reduced vancomycin susceptibility results in reduced transcription of *mecA* and increased susceptibility to β-lactams [14]. In a retrospective cohort monocentric study of patients with MRSA bacteremia, those who received vancomycin plus one β-lactam were more likely to experience microbiological eradication of MRSA than patients who received vancomycin alone [14]. More recently, in a pilot multicenter RCT for MRSA bacteremia [15], patients received vancomycin 1.5 g IV twice daily and were randomly assigned to flucloxacillin 2 g IV 6 hourly for 7 days or no additional therapy. The combination therapy group showed shorter duration of MRSA bacteremia and there was no difference in 28- and 90-day mortality, metastatic infection, nephrotoxicity, or hepatotoxicity (Table 1).

Lastly, both active and passive immunotherapy against *S. aureus* are undergoing intense research efforts. Unfortunately, almost all attempts to provide active immunization against *S. aureus* failed and experts wonder if such an approach may result in clinical implications. Nonspecific passive immunotherapy has been reported to be useful in the control of the effect of *S. aureus* exotoxin such as Panton-Valentine leukocidin which may be responsible for very severe forms of infections. Experts currently recommend the combination of high dose nonspecific human immunoglobulins with an antibiotic able to downregulate its production such as clindamycin, rifampin, or linezolid [16]. Biotechnologies resulted in the production of highly specific human monoclonal antibodies. Those targeted at *S. aureus* toxin A, with efficacy against both MSSA and MRSA, seem very promising and their use, either as prophylaxis (MEDI4893: NCT02296320) [17] or adjunctive treatment (AR-301: NCT01589185) of *S. aureus* infections, is currently under investigation in multicenter phase II clinical studies.

In conclusion, in the critically ill patient, individualized dosing of vancomycin, aiming at an AUC/MIC $\geq$ 400, and therefore with monitoring of serum levels and information about the Etest vancomycin MIC, is the correct strategy for vancomycin use. In MRSA HAP/VAP and in MRSA bacteremia, linezolid and daptomycin may be preferable, respectively, especially in high MIC MRSA and, in the case of daptomycin, using high dose and combination therapy. In difficult-to-treat MRSA bacteremia cases, combination of vancomycin or daptomycin with an anti-staphylococcal β-lactam may improve results in terms of microbiological eradication.

Author details
[1] Department of Emergency and Intensive Care, Faculty of Medicine, Grupo de Infecçao e Sepsis, Centro Hospitalar Sao Joao, University of Porto, Porto, Portugal. [2] Department of Emergency and Intensive Care, Faculty of Biology and Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.

Received: 24 August 2016 Accepted: 22 September 2016
Published online: 04 October 2016

References

1. de Gatte MDMF, Revilla N, Calvo MV, Dominquez-Gil A, Sanchez-Navarro A (2007) Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 33:279–285
2. Rybak MJ, Lomaestro BM, Rotscahfer JC, Moellering RC et al (2009) Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 49:325–327
3. Van Hal SJ, Lodise TP, Paterson DL (2012) The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis 54:755–771
4. Holmes NE, Turnidge JD, Munckhof WJ et al (2011) Antibiotic choice may not explain poorer outcomes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis 204(3):340–347
5. Cataldo MA, Tacconelli E, Grilli E, Pea F, Petrosillo N (2012) Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis. J Antimicrob Chemother 67(1):17–24
6. Liu C, Bayer A, Cosgrove SE et al (2011) 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 52(3):e18–e55
7. Wunderink RG, Niederman MS, Kollef MH et al (2012) Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis 54(5):621–629
8. Jiang H, Tang RN, Wang J (2013) Linezolid versus vancomycin or teicoplanin for nosocomial pneumonia: meta-analysis of randomized controlled trials. Eur J Clin Microbiol Infect Dis 32(9):1121–1128
9. Murray KP, Zhao JJ, Davis SL et al (2013) Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration > 1 mg/L: a matched cohort study. Clin Infect Dis 56:1562–1569
10. Gould IM, Miró JM, Rybak MJ (2013) Daptomycin: the role of high-dose and combination therapy for Gram-positive infections. Int J Antimicrob Agents 42(3):202–210
11. Schweizer ML, Furuno JP, Harris AD et al (2011) Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin susceptible *Staphylococcus aureus* bacteremia. BMC Infect Dis 11:279
12. Holmes NE, Tong SYC, Davis JS, van Hal SJ (2015) Treatment of methicillin-resistant *Staphylococcus aureus*: vancomycin and beyond. Semin Respir Crit Care Med 36:17–30
13. Montravers P, Dupont H, Bedos J-P et al (2014) Tigecycline use in critically ill patients: a multicentre prospective observational study in the intensive care setting. Intensive Care Med 40:988–997
14. Dilworth TJ, Ibrahim O, Hall P, Sliwinski J et al (2014) β-Lactams enhance vancomycin activity against methicillin-resistant *Staphylococcus aureus* bacteremia compared to vancomycin alone. Antimicrob Agents Chemother 58:102–109
15. Davis JS, Sud A, O'Sullivan MV, Robinson JO et al (2016) Combination of vancomycin and β-Lactam therapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a pilot multicenter randomized controlled trial. Clin Infect Dis 62(2):173–180
16. Gillet Y, Dumitrescu O, Tristan A, Dauwalder O et al (2011) Pragmatic management of Panton-Valentine leukocidin-associated staphylococcal diseases. Int J Antimicrob Agents 38(6):457–464
17. François B, Chastre J, Eggiman P, Laterre PF et al (2016) The SAATELLITE and EVADE clinical studies within the COMBACTE consortium: a public-private collaborative effort in designing and performing clinical trials for novel antibacterial drugs to prevent nosocomial pneumonia. Clin Infect Dis 63(Suppl 2):S46–S51