Enterococci

The MIC for dalbavancin against vancomycin-susceptible enterococci remains low for *Enterococcus faecalis* (MIC_{90}, 0.06 mg/l) and *E. faecium* (MIC_{90}, 0.12 mg/l) but falls into a wider range of ≤ 0.015–4 mg/l (Candiani *et al.*, 1999; Jones *et al.*, 2001; Streit *et al.*, 2004; Gales *et al.*, 2005; Jones *et al.*, 2005; Biedenbach *et al.,* 2009; Zhanel *et al.,* 2010). The values escalate drastically to an MIC_{90} of 32 mg/l for vancomycin-resistant strains of *E. faecalis* (MIC range, 0.015 to > 32 mg/l) and *E. faecium* (MIC range, 0.03 to > 32 mg/l) (Zhanel *et al.,* 2010). Dalbavancin does not demonstrate activity against VRE strains with vanA-mediated resistance (MIC_{90}, 32 mg/l), which display a high level of resistance to both vancomycin and teicoplanin (Malabarba and Goldstein, 2005; Streit *et al.*, 2005). It does maintain potent activity for vanB phenotypes (MIC_{90}, 0.12 mg/l), which also retain teicoplanin susceptibility. Against quinupristin–dalfopristin resistant *E. faecium* strains, dalbavancin has a potent MIC_{90} < 0.12 mg/l (Streit *et al.*, 2005). For vancomycin-susceptible and non-vanA *Enterococcus* spp., dalbavancin is more potent than telavancin but not oritavancin, which alternatively have activity against vanA-producing strains (Zhanel *et al.,* 2010).

OTHER GRAM-POSITIVE AEROBES AND ANAEROBES

Dalbavancin is potent against less common Gram-positive aerobes such as *Bacillus* spp., *Corynebacterium* spp., *Listeria* spp., and *Micrococcus* spp., with MIC_{90} values (0.016–0.25 mg/l) that are comparable with vancomycin, linezolid, daptomycin, and quinupristin–dalfopristin (Jones *et al.*, 2001; Goldstein *et al.*, 2003; Streit *et al.*, 2004; Gales *et al.*, 2005; Jones *et al.*, 2005; Goldstein *et al.*, 2006; Heine *et al.*, 2010; Jones and Stilwell, 2013; Rolston *et al.,* 2015). It is generally two- to fourfold more potent than vancomycin against Gram-positive anaerobes such as *Actinomyces* spp. (MIC_{90}, 0.5 mg/l), *Eubacterium* spp. (MIC_{90}, 1 mg/l), *Propionibacterium* spp. (MIC_{90}, 0.5 mg/l), and *Peptostreptococcus* spp. (MIC_{90}, 0.25 mg/l) (Goldstein *et al.*, 2003). However, for *Clostridium difficile*, dalbavancin (MIC_{90}, 2 mg/l; MIC range ≤ 0.015–8) is less potent than vancomycin and metronidazole (Goldstein *et al.*, 2006). *Lactobacillus* spp. also demonstrate dalbavancin resistance with an MIC_{90} > 32 mg/l for *Lactobacillus acidophilus* and *L. casei*, although *L. fermentans* is easily inhibited by an MIC ≤ 0.25 mg/l (Goldstein *et al.,* 2003).

2b. Emerging resistance and cross-resistance

Dalbavancin MIC results within the past 10 years against US Gram-positive pathogens remain consistent and do not indicate MIC change or emerging resistances among analyzed isolates (Jones *et al.,* 2013a; Jones *et al.,* 2013b). Population data of more than 1100 staphylococci and 300 beta-hemolytic streptococci isolates from US medical centers in 2011 demonstrated only 3 staphylococcal isolates (0.3%), and 14 streptococcal isolates (4%) possessed dalbavancin MIC values above the current FDA/European Committee on Antimicrobial Susceptibility Testing breakpoint (Jones *et al.,* 2013a). However, as mentioned earlier, dalbavancin demonstrates diminished activity against VRE and VRSA isolates expressing VanA, which is a common glycopeptide-resistant phenotype. Resistance arises via alteration of peptidoglycan precursors, such that pentapeptides normally terminating in D-alanine-D-alanine are revised to terminate in D-alanine-D-lactate or D-alanine-D-serine, potentially decreasing antibiotic target affinity up to 100-fold (Malabarba and Ciabatti, 2001; Courvalin, 2006; Bailey and Summers, 2008; Zhanel *et al.,* 2010).

Studies suggest that staphylococci are less likely to develop resistance to dalbavancin than to vancomycin and teicoplanin. In a study by Lopez *et al.* (2005), no single-step resistance (frequency < 10^{-10}) was detected for dalbavancin when *S. aureus* was incubated on plates containing 10 mg/l of dalbavancin, 10 mg/l of vancomycin, and 15 mg/l of teicoplanin. After 24 serial passages through sub-MIC concentrations, dalbavancin MIC increased twofold for *S. aureus*, whereas greater increases were seen with vancomycin (fourfold) and teicoplanin (eightfold). In another study with six strains of *Staphylococcus* spp. (containing methicillin-resistant and vancomycin-intermediate isolates), single-step resistance was not encountered when incubated at 0.5, 1, 2, 4, and 8 times MIC of dalbavancin (Goldstein *et al.*, 2007). After 20 serial passages, four strains had equal or double the MIC, whereas two methicillin-resistant strains had a four- to sixfold increase. Susceptibility was reinstated after the isolates were grown on a drug-free medium for 3 days.

3. MECHANISM OF DRUG ACTION

Like other glycopeptides, dalbavancin inhibits the final stages of peptidoglycan synthesis by forming a binding pocket with the D-alanyl-D-alanine terminus of peptidoglycan precursors (Van Bambeke, 2004; Van Bambeke *et al.*, 2004; Kahne *et al.*, 2005; Malabarba and Goldstein, 2005). The complex created between the heptapeptide backbone and the D-alanyl-D-alanine dipeptide blocks access for transglycosylases and transpeptidases, enzymes that are necessary to pursue polymerization and cross-linking. As a result, the nascent peptidoglycan chain is halted from developing further, leaving cells vulnerable to rupture from changing internal osmotic pressure.

The addition of a lipophilic side chain seems to afford dalbavancin more ways to improve the interaction with D-alanyl-D-alanine peptides (Beauregard *et al.*, 1995; Kahne *et al.*, 2005; Malabarba and Goldstein, 2005). It is hypothesized to allow for dimerization (like vancomycin) and membrane anchoring (like teicoplanin), which increases dalbavancin's binding affinity to the hydrophobic target site, more so than vancomycin (Treviño *et al.*, 2014). Homodimers formed between glycopeptide molecules lock the binding pocket into a prime position to facilitate cooperative binding (Van Bambeke, 2004; Van Bambeke *et al.*, 2004). Membrane anchoring helps localize dalbavancin closer to its target.