



## How can we improve the use of lipopeptides?

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Lipopeptides are a class of agents with excellent antibacterial activity. Daptomycin, telavancin and vancomycin are active against gram-positive pathogens, and the polymyxins (polymyxin B and colistin) have potent gram-negative activity. Our research group has a primary focus of examining the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobial agents, as they relate to the optimal treatment of infectious diseases and suppression of resistance development. In this presentation, basic PK/PD concepts will be briefly reviewed. We will examine contemporary literature with respect to the experimental / clinical evidence supporting drug dosing based on PK/PD. Finally, the potential to minimize toxicity and resistance development will also be discussed. Highlights of the presentation are as follow.

### Daptomycin

Daptomycin was first developed in the 1970's but abandoned by its original developer because of toxicity concerns. With a better understanding of pharmacokinetics / pharmacodynamics, the exact same agent was re-developed. Daptomycin has been shown to exhibit concentration-dependent killing in a pre-clinical infection model and AUC/MIC was the PK/PD variable most closely linked to killing (Louie, 2001), thus dosing frequency was not expected to contribute substantially to its overall effect. After almost 30 years, the agent was finally approved by the FDA for clinical use in 2003 employing only a different (once-daily, weight-based) dosing regimen. Muscle toxicity remains a concern for many clinicians. Recently, the likelihood of experiencing elevations in the creatine phosphokinase (CPK) level has been linked to daptomycin exposures, in patients with *S. aureus* bacteremia (Bhavnani, 2010). A significant relationship between the minimum concentration of daptomycin and the probability of CPK elevation was reported. Collectively, these data are expected to further guide the optimal dosing of daptomycin, balancing clinical efficacy and toxicity.

## Vancomycin

In view of its spectrum of activity and cost, vancomycin is likely the most common antimicrobial agent used for the treatment of MRSA infections worldwide. Despite decades of clinical use, the PK/PD of vancomycin are not fully appreciated. Clinical data suggest that more favorable clinical outcomes are observed in lower respiratory tract infections if the AUC/MIC achieved is  $\geq 400$  (Moise-Broder, 2004), and high trough levels (15-20 mg/L) are advocated for the treatment of nosocomial pneumonia (ATS/IDSA, 2005). Based on the best data available, a consensus on the therapeutic monitoring of vancomycin has been recently published (Rybak, 2009). The nephrotoxic potential of vancomycin remains controversial. Toxicities observed with early studies have been attributed to the impurities of the pharmaceutical formulations. However, a high daily dose ( $\geq 4$  grams daily) has been linked to a higher incidence of nephrotoxicity in the contemporary literature (Lodise, 2008). Limited clinical data suggest that the onset of nephrotoxicity associated with prolonged therapy may be delayed by continuous infusions of vancomycin (Ingram, 2009), but the clinical utility of routine vancomycin continuous infusion remains to be validated in prospective randomized studies.

## Polymyxin B

The polymyxins are increasingly used clinically due to the emergence of multidrug resistance in gram-negative bacteria. The properties of these agents are also poorly understood, which represents a major hindrance to optimal clinical use. Resistance to polymyxin B has been reported and appears to be related to suboptimal use. With ongoing investigations, there is much room to improve the clinical use of polymyxin B (Yuan, 2008).

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