

Kiang, T. K. et al. (2014). "A comprehensive review on the pharmacokinetics of antibiotics in interstitial fluid spaces in humans: Implications on dosing and clinical pharmacokinetic monitoring." *Clin Pharmacokinet* 53(8):695–730.

The objective of the current review was to provide an updated and comprehensive summary on pharmacokinetic data describing the distribution of antimicrobials into interstitial fluid (ISF) by comparing drug concentration versus time profiles between ISF and blood/plasma in healthy individuals and/or diseased populations. An extensive literature search identified 55 studies detailing 87 individual comparisons. For each antibiotic (antibacterial) (or antibiotic class), we comment on dosing implications based on tissue ISF distribution characteristics and determine the suitability of conducting clinical pharmacokinetic monitoring (CPM) using a previously published scoring algorithm. Using piperacillin as an example, there is evidence supporting different degrees of drug penetration into the ISF of different tissues. A higher dose of piperacillin may be required to achieve an adequate ISF concentration in soft tissue infections. To achieve these higher doses, alternative administration regimens such as intravenous infusions may be utilized. Data also suggest that piperacillin can be categorized as a 'likely suitable' agent for CPM in ISF. Regression analyses of data from the published studies, including protein binding, molecular weight, and predicted partition coefficient (using  $Xlog P3$ ) as dependent variables, indicated that protein binding was the only significant predictor for the extent of drug distribution as determined by ratios of the area under the concentration–time curve between muscle ISF/total plasma ( $R(2) = 0.65, p < 0.001$ ) and adipose ISF/total plasma ( $R(2) = 0.48, p < 0.004$ ). Although recurrent limitations (i.e., small sample size, lack of statistical comparisons, lack of steady-state conditions, high individual variability) were identified in many studies, these data are still valuable and allowed us to generate general dosing guidelines and assess the suitability of using ISF for CPM.

Kiem, S. and J. J. Schentag (2014). "Interpretation of epithelial lining fluid concentrations of antibiotics against methicillin resistant staphylococcus aureus." *Infect Chemother* 46(4):219–225.

Although antibiotics whose epithelial lining fluid (ELF) concentrations are reported high tend to be preferred in treatment of pneumonia, measurement of ELF concentrations of antibiotics could be misled by contamination from lysis of ELF cells and technical errors of bronchoalveolar lavage (BAL). In this review, ELF concentrations of antimethicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics were interpreted considering above confounding factors. An equation used to explain antibiotic diffusion into CSF (cerebrospinal fluid) was adopted:  $\text{ELF/free serum concentration ratio} = 0.96 + 0.091 \times \ln(\text{partition coefficient/molecular weight}(1/2))$ . Seven anti-MRSA antibiotics with reported ELF concentrations were fitted to this equation to see if their ELF concentrations were explainable by the penetration capacity only. Then, outliers were modeled under the assumption of varying contamination from lysed ELF cells (test range 0%–10% of ELF volume). ELF concentrations of oritavancin, telavancin, tigecycline, and vancomycin were well described by the diffusion equation, with or without additional impact from cell lysis. For modestly high ELF/free serum concentration ratio of linezolid, technical errors of BAL should be excluded. Although teicoplanin and iclaprim showed high ELF/free serum ratios also, their protein binding levels need to be cleared for proper interpretation. At the moment, it appears very premature to use ELF concentrations of anti-MRSA antibiotics as a relevant guide for treatment of lung infections by MRSA.