# Presentation Title

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**Scope of the lecture:**
Therapeutic Drug Monitoring of Beta-lactams

**Learning objectives:**
1. Describe the rationale and settings for applying beta-lactam TDM
2. Outline current PK-PD targets ranges that are utilized for TDM of beta-lactams
3. Discuss the need and importance of future research in this area

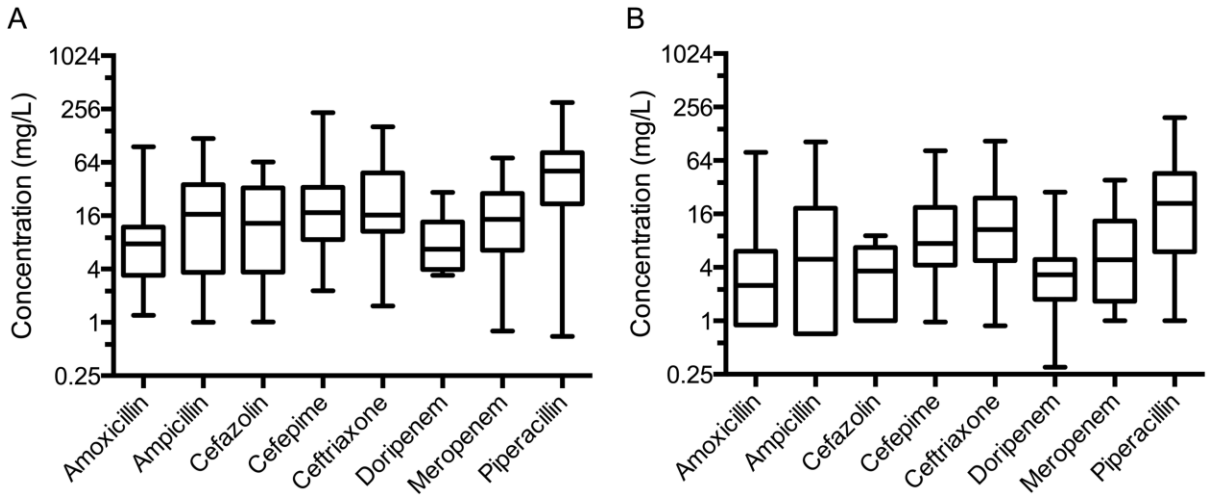
**Extended abstract:**

Beta-lactams are one of the most commonly prescribed antibiotic classes in the world, with estimates suggesting that they represent nearly 65% of antibiotic use. Beta-lactams consist of narrow-spectrum penicillins, cephalosporins, monobactams, extended-spectrum penicillins and carbapenems.

Although beta-lactams have been used for more than 70 years in the treatment and prevention of infections, there has been relatively little exploration of dose optimisation, especially in patients at high risk of dying from infections treated with these antibiotics. Like many other drugs, doses extrapolated from pre-clinical data have been in human studies, primarily in healthy volunteers, to determine beta-lactam dosing regimens. However, it is questionable as to whether these standard dosing regimens are universally appropriate across all patient groups.

For example, patients such as the critically ill, the obese and those with renal or hepatic failure are among the patient population for which challenges in establishing optimal dosing strategies still exist. Due to a myriad of factors causing altered pharmacokinetics, there can be wide inter- and intra-patient variability in exposures to drugs such as the beta-lactams.

The DALI (Defining Antibiotic Levels in Intensive care unit (ICU) patients) Study,[1] a prospective, multinational pharmacokinetic point-prevalence study conducted in over 380 critically ill patients showed up to a 500-fold variation in unbound concentrations of commonly used beta-lactams using contemporary dosing regimens (**Figure 1**[1]). Study investigators concluded that more personalized dosing of beta-lactams in the critically ill is required to ensure safety as well as efficacy.




*Source: Roberts JA, Paul SK, Akova M, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;58:1072-83.*

Another challenge to ensuring optimal beta-lactam dosing, especially in the critically ill population group, is the decreased bacterial susceptibility to these antibiotics often observed in the ICU. A number of studies have shown that pathogens isolated in the ICU often have significantly higher minimum inhibitory concentrations (MICs) than those isolated outside of the ICU,[2-4] providing further argument that targeted beta-lactam dosing is required.

Beta-lactams exhibit maximum bactericidal activity when unbound concentrations of the drug exceed the minimum inhibitory concentration (MIC) of the bacterial pathogen ($fT_{>MIC}$). Known as time-dependent killing, beta-lactam dose optimisation usually involves more frequent dosing and/or the use of extended or continuous infusions, so as to maintain unbound concentrations above the MIC. The only method of verifying that beta-lactam concentrations are likely to be safe and effective is through the use of therapeutic drug monitoring (TDM).

There are many challenges in developing TDM for beta-lactams, one of which is to determine what type of drug assay should be used. It is known that the free or 'unbound' concentration of the antibiotic is available for biological/microbiological activity. Therefore, developing beta-lactam drug assays that measure total antibiotic concentrations may not always be accurate, especially for highly protein-bound beta-lactams and in patients exhibiting significant variability in plasma protein concentrations, such as critically ill patients.[5]

Secondly, there is a lack of concensus in the literature regarding optimal beta-lactam pharmacokinetic-pharmacodynamic (PK-PD) targets. In some clinical studies, PK-PD targets associated with microbiogical eradication have been shown to correlate with unbound plasma concentrations maintained four to six times above the MIC throughout the entire dosing interval (i.e. 100% $fT_{>4\text{-}6xMIC}$).[6-8] Other pre-clinical data have shown maximal bactericidal effect occurs for only a proportion of, rather than the entire dosing interval. Based on this, targets for unbound concentrations remaining four times above the MIC (4xMIC) for 50%, 70% and 40% for the penicillins, cephalosporins and carbapenems, respectively, have been stipulated.[9] Hence, a suggested PK-PD endpoint of unbound plasma concentrations above the MIC for the entire dosing interval (i.e. 100% $fT_{>1xMIC}$) has been suggested as ensuring that 40-70% $fT_{>4xMIC}$ will be achieved.[10] Of note, MICs used to determine PK-PD targets may either be derived directly from clinical/pathogen isolates or, if culture negative, from clinical breakpoints determined by antimicrobial susceptibility testing centers.

Results from a 2014 survey of beta-lactam TDM practices in ICUs across the world have revealed that this alternative PK-PD target is most frequently aimed for.[11] However, whether 100% $fT_{>1xMIC}$ ensures 40-70% $fT_{>4xMIC}$ has recently been challenged, with a recent study using first-dose simulations suggesting that only a small number of patients will achieve 40-70% $fT_{>4xMIC}$ (for beta-lactams such as piperacillin, ceftazidime and cefepime) if a PK-PD target of 100% $fT_{>1xMIC}$ is aimed for.[12]

There are currently two administration methods of administering beta-lactam antibiotics, with intermittent bolus dosing being the traditional approach to administering these antibiotics and prolonged/continuous infusions gaining momentum as a dose optimization strategy. However, with intermittent bolus dosing, there is still some conjecture on the optimal PK-PD target, with 100% $fT_{>4\text{-}6xMIC}$ versus 100% $fT_{>1xMIC}$ being the two main PK-PD endpoints aimed for. A steady-state unbound concentration 4xMIC is generally accepted as the PK-PD target of choice for beta-lactams administered via continuous infusion.

Besides the use of TDM for efficacy, beta-lactam exposure related toxicity is also an important consideration, especially in patients where acute and dramatic changes in drug clearances can result in rapid accumulation. A recent retrospective study by Imani and colleagues have provided some sound preliminary data on which to identify toxicodynamic thresholds.[13] Based on their review of TDM results and related adverse events in a group of 378 patients treated with either meropenem, piperacillin or flucloxacillin, these investigators

found threshold concentrations for which there was a 50% risk of developing the beta-lactam associated toxicities of neurotoxicity and nephrotoxicity.

For neurotoxicity, unbound plasma trough concentration ($C_{min}$) thresholds of >361.4 mg/L for piperacillin, >64.2 mg/L for meropenem, and >125.1 mg/L for flucloxacillin were identified. Whilst for nephrotoxicity, >452.65 mg/L for piperacillin and 44.45 mg/L for meropenem were determined. Given that the MIC clinical breakpoints are 16 mg/L, 2mg/L and 2mg/L for piperacillin, meropenem and flucloxacillin, respecitively,[14] these $C_{min}$ toxicity thresholds are between 20 to 60 times above susceptibility breakpoints, indicating a generally broad therapeutic index for the selected exposure-related toxicities.

Perhaps unsurprisingly, use of a TDM-guided dosage adjustment strategy to achieve PK-PD targets has shown some promise. When compared to empiric-based dosage adjustment, De Waele and colleagues showed that TDM-guided dosage adjustment was more likely to achieve PK-PD targets when dose optimising for meropenem and piperacillin in a small group of critically ill patients.[15] After 72 hours of beta-lactam therapy, target attainment rates for 100 % $fT_{>4xMIC}$ and 100 % $fT_{>1xMIC}$ were higher in the TDM-based dosage adjustment group: 58% vs 16 %, $p = 0.007$ and 95 vs 68 %, $p = 0.045$, respectively. Interestingly, even with the use of TDM-guided dosage adjustment, the higher PK-PD target of 100 % $fT_{>4xMIC}$ was achieved in less than 60% of patients randomised into this group, highlighting the challenges of attaining this more demanding target.

Conclusions

TDM of beta-lactam antibiotics provides the next logical step to improve dose optimisation of this important group of antibiotics, particularly in the setting of altered pharmacokinetics and changes in pathogen susceptibility. Although data to date provides some good guidance on how beta-lactam exposures can relate to effect, there is still a need for robust prospective data to better define PK-PD targets, especially in high-risk groups.

Use of TDM-guided dosing intuitively ‘makes sense’, but further work is required to determine the most efficient method to dose optimise and we are still awaiting outcome data quantifying the patient-centred benefits of using this type of strategy.

**References**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