Updates on
Antimicrobial Stewardship
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Understanding and Interpreting Pharmacokinetic (PK) and Pharmacodynamic (PD) Targets for Antimicrobial Dosing

Back to Basics – a reminder of PK/PD

PK describes the movement of drug through the body over time - influenced by its absorption, distribution, metabolism and excretion.

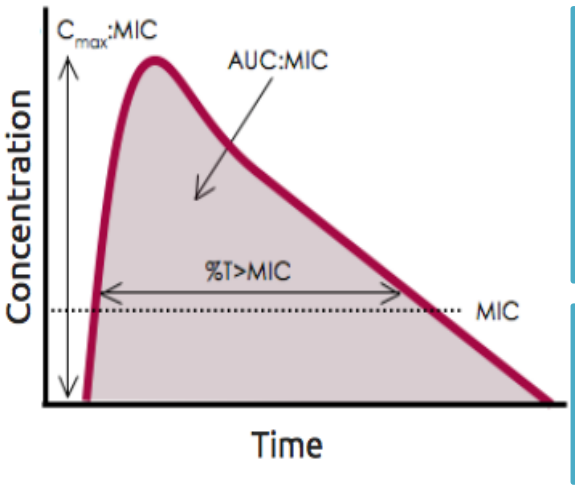
- Physiological factors which can influence this include gastrointestinal conditions, drug/food interactions, renal function, volume of distribution and the site of infection
- Drug factors which can influence this include lipophilicity of the drug, bioavailability and protein binding

PD is the study of effect (efficacy and toxicity) once the drug has reached a specified site of action. In the case of antimicrobials this is the ability to kill or inhibit antimicrobial growth once at the site of action.

Time-dependent versus Concentration-dependent activity

Different antimicrobials have different mechanisms of action and bactericidal activity characteristics. The efficacy of an antimicrobial is determined by a range of factors including activity and duration of effect at the site of infection (known as the PK-PD indice) and MIC as outlined below.

The PK-PD indices associated with antibacterial activity



Time (%T) > MIC = Time-dependent antimicrobials

Effect depends on duration the unbound drug is at concentrations above the MIC

- Increasing the frequency of dosing or giving via continuous infusion will increase %T > MIC
- Increasing dose to achieve higher concentrations does not result in greater efficacy once it is above the MIC

AUC:MIC = Concentration-dependent antimicrobials with time dependence

Effect is related to the AUC of the unbound drug from 0-24 hours and the MIC

Cmax:MIC = Concentration-dependent antimicrobials

Greater killing achieved as the ratio of drug concentration (Cmax) to MIC increases within the therapeutic range

- Changing the dose will mainly alter the Cmax:MIC and AUC:MIC ratio
- Larger doses, less frequently improve chances of success

Pharmacodynamic index correlated with maximal efficacy of selected antimicrobials:

Antimicrobial / Class	Effect	Distribution	Excretion	PK/PD parameter
Beta-lactams (includes Carbapenems)	Bactericidal	Low protein binding + hydrophilic	Renal	Time > MIC
Aminoglycosides	Bactericidal	Hydrophilic	Renal	Cmax:MIC & AUC:MIC
Vancomycin	Bactericidal	Hydrophilic	Renal	AUC:MIC
Linezolid	Bacteriostatic	Lipophilic wide distribution	Renal / Non-renal	AUC:MIC
Clindamycin	Bacteriostatic	Lipophilic wide distribution	Hepatobiliary	AUC:MIC
Daptomycin	Bactericidal	Highly protein bound (weak, reversible) + hydrophilic	Renal	Cmax:MIC & AUC:MIC
Fluoroquinolones (e.g. ciprofloxacin)	Bactericidal	Lipophilic wide distribution	Renal & hepatobiliary	Cmax:MIC & AUC:MIC

Where should we be considering PK/PD?

Hypoalbuminaemia

- Leads to more unbound drug available causing temporarily higher drug concentrations
- Is usually associated with ↑ Vd & drug clearance of highly protein bound hydrophilic drugs so free drug is diluted through total body water and rapidly cleared
- Patients may need higher loading & maintenance doses of these antimicrobials

Obesity

- This will be covered in a future issue

CNS Infections

- Penetration into CSF determined by molecular size, lipophilicity and protein binding
- ↑ in permeability of blood-CSF/blood brain barrier and ↓ in CSF flow leading to ↑ drug concentrations during inflammation

Critical Illness

- Multi-organ failure changes absorption, distribution, metabolism and excretion of drugs
- Changes to pH, protein binding and interstitial fluid shifts affects drug distributions especially of mainly hydrophilic drugs with low Vd

Renal Function

- Especially important for hydrophilic antimicrobials which are almost entirely renally cleared
- Vd increased in patients with moderate to severe CKD due to reduced protein binding, increased tissue binding +/or fluid overload
- Impact of dialysis on PK/PD depends on type of dialysis, molecular weight, protein binding and Vd of the drug

Burns

- Area and depth of burn, presence of sepsis, dehydration & time since injury all affect PK
- Hypometabolic state in first 48hrs post burn due to reduced cardiac output & tissue perfusion & therefore decreased metabolism/clearance of drugs
- Hypermetabolic state after 48hrs resulting in ↑ cardiac output & tissue perfusion hence increased metabolism/clearance of drugs

Vd = volume of distribution
CKD = chronic kidney disease
CSF = cerebrospinal fluid

References / Further reading:

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2. Shah, S, Barton G, Fischer A. Pharmacokinetic considerations and dosing strategies of antibiotics in the critically ill patient. Journal of the Intensive Care Society. 2015; 16(2):147-153.
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Produced by the Central Adelaide Local Health Network (CALHN) Antimicrobial Stewardship Committee

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