THE APPLICATION OF PHARMACODYNAMICS IN THE OPTIMIZATION OF ANTIBIOTIC THERAPY

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Pharmacokinetic/pharmacodynamic considerations

- The goal of antibiotic therapy is to achieve complete bacterial eradication and to minimize the risk of resistance selection.
- The dosing regimen for a particular antibiotic is influenced by its pharmacokinetic (PK) profile and the susceptibility of the target pathogen.
- PK/PD models can be used to predict bacteriological and clinical efficacy and help to identify the correct dose and dosing interval.

PK/PD considerations

- The bactericidal activity of an antibiotic can be time or concentration dependent.
- Bacteriological efficacy also depends on the persistence of the drug effect after serum levels have fallen below the minimum inhibitory concentration (MIC) for the target pathogen (post-antibiotic effect (PAE)).
- Prolonged exposure to suboptimal concentrations of antibiotics can lead to incomplete bacterial eradication and selection of resistance.
- Penetration into target tissues is very important.

PD profiling of antibiotics

- Time-dependent killing
  - time above MIC (T>MIC)
- Concentration-dependent killing
  - area under the concentration-time curve (AUC)/MIC ratio
  - peak serum concentration (Cmax)/MIC ratio
- PAE

THE CONCEPT of SEPTIC CLOCK

INITIAL RESUSCITATION

- SpO2 > 95%: 10 min
- Antibiotics: 60 min
- MAP > 70 mm Hg: 20 min
- Source identification: 60 min
- Svo2 (Scvo2) > 70%: 60 min
- Heart rate: Urine output

Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis: Antibiotic Therapy

Prompt initiation of appropriate therapy with antibiotics is essential to minimize morbidity and mortality. The dosing regimen for a particular antibiotic should be determined by the susceptibility of target pathogen and by its pharmacokinetic profile.
**β-Lactams**

- High or frequent dosing is used to optimise T>MIC and improve clinical response and bacteriological eradication.
- May incur increased labour and drug costs.
- Based on PD profiling, the antibiotic with the best in vivo potency can be selected by integrating available microbiological potency data and the PK profile of the agent(s) concerned.
- Prolongation of administration can enhance the PK profile of these agents.


**Resistance prevention**

Use PK/PD considerations to optimise the bacterial killing potential of antibiotic therapy.

Dead bugs don’t mutate!


**Aminoglycosides**

- $C_{\text{max}}$/MIC ≥ 10 translates into improvements in the rate and extent of clinical response.
- Once-daily administration is advocated to maximise efficacy and minimise potential drug accumulation and toxicity.


**Summary**

- PK/PD considerations provide the opportunity for clinicians to prescribe currently available antibiotics according to regimens that maximise bacteriological eradication and clinical outcomes and minimise resistance selection, ie administration of appropriate antibiotics at the right dose for the appropriate duration.