THE APPLICATION OF PHARMACODYNAMICS IN THE OPTIMIZATION OF ANTIBIOTIC THERAPY

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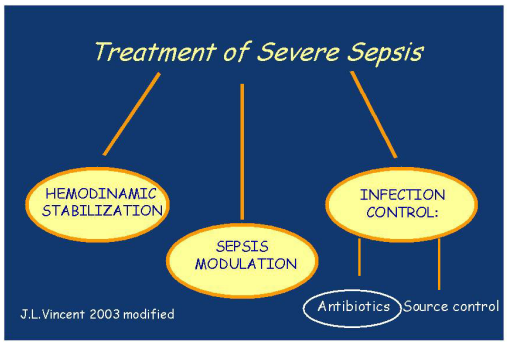


Pharmacokinetic/pharmacodynamic considerations

- The goal of antibiotic therapy is to achieve complete bacterial eradication and to minimise 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/pharmacodynamic (PD) models can be used to predict bacteriological and clinical efficacy and help to identify the correct dose and dosing interval

THE CONCEPT of SEPTIC CLOCK

INITIAL RESUSCITATION

SpO2 > 95%	10 min
Antibiotics	60 min
MAP > 70 mm Hg	20 min
Source identification	60 min
SvO_2 ($ScvO_2$) > 70%	60 min
Heart rate	
Urine output	

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

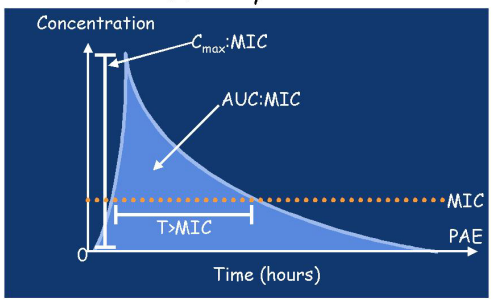
Surviving Sepsis Company Guidelines for Management of Severe Sepsis: Antibiotic Therapy

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

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 (C_{max}):MIC ratio
- PAE

PK/PD parameters affecting antibiotic efficacy *in vivo*



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 PD profile of these agents

Nicolau et al. Antimicrob Agents Chemother 2000;44:1291–1295
Craig & Andes. Pediatr Infect Dis J 1996;15:255–259
Grant et al. Pharmacotherapy 2002;22:471–483

Pharmacodynamic Parameters Predictive of Outcome

Parameter Correlating With Efficacy	C_{max}: MIC	AUC:MIC	T > MIC
Examples	Aminoglycosides Fluoroquinolones	Azithromycin Fluoroquinolones Ketolides	Carbapenems Cephalosporins Macrolides Penicillins
Organism kill	Concentration dependent	Concentration dependent	Time dependent
Therapeutic goal	Maximize exposure	Maximize exposure	Optimize duration of exposure

Drusano and Craig. *J Chemother.* 1997;9:38-44.
Drusano et al. *Clin Microbiol Infect.* 1998;4(suppl 2):S27-S41.
Vesga et al. 37th Annual ICAAC. Abstract F-255.

β-Lactams: optimising exposure

- The optimum level of exposure varies for different agents within the β-lactam class: approximately T>MIC of:
  - ~ 60–70% for cephalosporins
  - ~ 50% for penicillins
  - ~ 40% for carbapenems

Drusano. Clin Infect Dis 2003;36(Suppl. 1):S42–S50

Resistance prevention

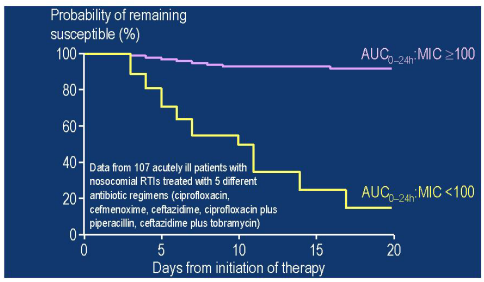
Use PK/PD considerations to optimise the bacterial killing potential of antibiotic therapy
Dead bugs don't mutate!

Aminoglycosides

- C_{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

Moore et al. J Infect Dis 1987;155:93–99
Kashuba et al. Antimicrob Agents Chemother 1999;43:623–629
Nicolau et al. Antimicrob Agents Chemother 1995;39:650–655

Probability of developing resistance



Thomas et al. Antimicrob Agents Chemother 1998;42:521–527

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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