UNIVERSITY of MARYLAND

Pharmacokinetics and Pharmacodynamics of Antimicrobials in Sepsis

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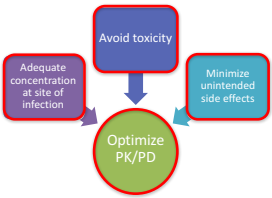
Objectives

1) Review the goals and terminologies of pharmacotherapy of antimicrobials in sepsis.
2) Describe how altered physiology in sepsis can impact antimicrobial pharmacokinetic (PK) and pharmacodynamic (PD) properties, with an emphasis on augmented renal clearance and renal dysfunction.
3) Characterize PK/PD targets of different antimicrobial classes.
4) Evaluate benefits and limitations of PK/PD strategies used to optimize antimicrobials in sepsis.

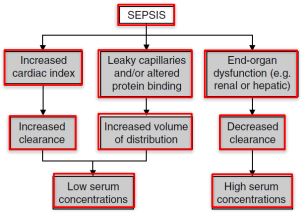
Goals of Pharmacotherapy



Key Terminologies

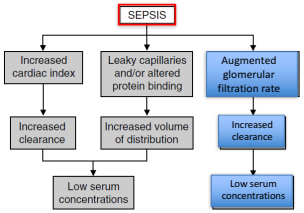
- Pharmacokinetics A D M E
  Processes conducted by the body on the drug
- Pharmacodynamics
  Describes the pharmacologic response resulting from drug at the site of action
- Pharmacogenomics
  Patient-specific differences in PK/PD through genetic polymorphisms

Pathophysiologic Changes in Sepsis



Roberts JA, Lipman J. *Clin Pharmacokinet* 2006;45(8):755-773.

Pathophysiologic Changes in Sepsis



Roberts JA, Lipman J. *Clin Pharmacokinet* 2006;45(8):755-773.

Augmented Renal Clearance

- Increased glomerular filtration
- ? Role of tubular secretion and reabsorption
- Possibly a natural response to critical illness in patients with greater physiologic reserve
- No standard definition
  - Creatinine clearance (CrCl) > 120 – 150 mL/minute
- Requires urine creatinine collection for diagnosis
- Prevalence of 30-65% general ICU population
- Peaks between ICU day 4-5, normalizes around ICU day 7

Hobbs AL, et al. *Pharmacotherapy* 2015;35(11):1063-1075.

Augmented Renal Clearance

- **ICU factors**
  - Increased cardiac output
  - Increased blood flow to major organs
  - Fluid resuscitation increasing blood volume to afferent arteriole

Increased perfusion to kidneys

- **Patients with greatest risk**
  - Early phase sepsis
  - Major trauma
  - Traumatic brain injury
  - CNS infection
  - Ventilator associated pneumonia
  - Burn
  - Major surgery
  - Hematologic malignancy
  - Pregnancy

Hobbs AL, et al. *Pharmacotherapy* 2015;35(11):1063-1075.

Acute Kidney Injury (AKI)

- Kidney Disease: Improving Global Outcomes (KDIGO) society guidelines
  - Chronic kidney disease: adjust doses based on FDA-approved labeling
  - AKI: for hydrophilic medications
    - Administer loading dose 25-50% greater than normal
    - Provide normal or near normal maintenance dosage
- Guidance on dosing of specific medications not provided for AKI in FDA-approved labeling or KDIGO society guidelines

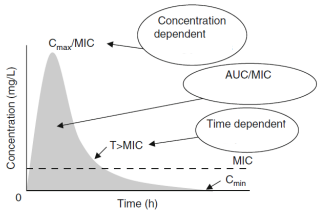
CLINICAL JUDGEMENT REQUIRED

Matzke GR, et al. *Kidney int* 2011;80:1122-37.

AKI – Practical Recommendations

- Monitor serum creatinine and urine output trends, consider urine creatinine collection
- Normal loading doses (fluconazole 800 mg in suspected fungemia)
- Err on the more aggressive approach, especially with antimicrobials in sepsis
- In dosing β-lactams, estimate CrCl 30-50 for AKI unless patient anuric (wide therapeutic index)
- Therapeutic drug monitoring as available, especially for narrow therapeutic index antimicrobials (aminoglycosides, vancomycin)

PK/PD Goals of Antimicrobials



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PK/PD Goals of Antimicrobials

Antibacterial	Kill Characteristic	Pharmacodynamic Goal
Aminoglycosides	Concentration dependent	C_{max}/MIC
Metronidazole		
Azithromycin	Concentration and time dependent	AUC/MIC
Tetracyclines		
Glycopeptides		
Fluoroquinolones		
Beta-Lactams	Time dependent	T>MIC
Linezolid		
Clarithromycin		
Clindamycin		

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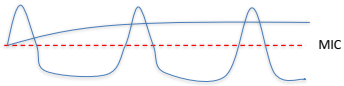
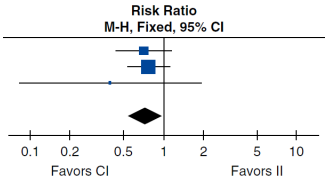
Continuous or Extended Infusion β-Lactams



Continuous or Extended Infusion β-Lactams



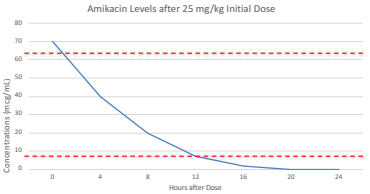
Roberts, JA et al. *Am J Respir Crit Care Med* 2016;194(6):681-691.

High Dose Extended Interval Aminoglycosides

- Aminoglycosides frequently given to cover multi-drug resistant Gram negative infections
- Relationship between C_{max} and MIC most important for efficacy
  - Optimal efficacy when C_{max} 8X - 10X ≥ MIC
  - Also consider site of infection
- C_{min} most important for toxicity
- Optimal dosing strategy → high dose extended interval aminoglycosides

Taccone FS, et al. *Am J Respir Crit Care Med* 2016;194(6):681-691.

High Dose Extended Interval Aminoglycosides

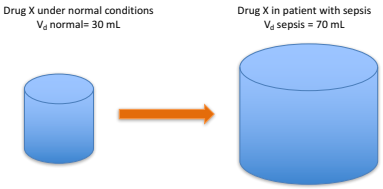


Antimicrobial Levels at Site of Infection

- Must assess whether drug is appropriate for site of infection
- Volume of distribution (V_d)
- Ability of drug to concentrate at site?
- Site of infection difficult to penetrate?
- If suboptimal PK/PD match for site of infection, must identify ways to optimize

Loading Doses in Critically Ill

V_d = Dose ÷ C_{max}



Loading Doses
Vancomycin Example

- V_d (wide range) 0.4 – 1 L/kg
- Critically ill patients, consensus statements suggest loading dose of 25 – 30 mg/kg (based on actual body weight)
  - Facilitates rapid achievement of target trough concentration
  - Overcomes increased V_d observed in sepsis

Rybak M, et al. *Am J Health-Syst Pharm* 2009;66:82-98.

Conclusions

- An understanding of PK/PD concepts is vital to optimal dosing of antimicrobials in septic patients
- Sepsis can cause changes in distribution and clearance of antimicrobials, based on the underlying pathophysiology for each individual patient and drug class
- Loading doses, continuous or extended infusions, and high doses given at extended intervals are examples of strategies to optimize PK/PD parameters of antimicrobials in patients with sepsis

Interprofessional Education Module to Learn, Teach, and Optimize the Treatment of Sepsis

- Jeffrey P. Gonzales, PharmD
- Nirav G. Shah, MD
- Renee Dixon, MD
- Joan M. Davenport, RN, PhD
- Mojdeh S. Heavner, PharmD
- Samuel A. Tisherman, MD
- Tracey Wilson, DNP
- Siu Yan Amy Yeung, PharmD
- Nimeet Kapoor, RN
- Peter P. Olivieri, MD