Antibiotic Pharmacokinetics in the ITU...an Update

Snehal Shah

Specialist Pharmacist - clinical services

and Dr John Vogel

What we will cover today

- Understanding the pathophysiological changes in critically ill patients
- Are we dosing our patients appropriately?
- Pharmacokinetics/dynamics of antibiotics
- Discuss specific antibiotic classes

Resistance - everyone is talking about it!

The Barcelona Declaration from the World Alliance against Antibiotic Resistance: engagement of

guardian.co.uk

The reason why this deadly E coli makes doctors shudder

It is past time for health authorities to curb the antibiotic misuse that created the resistance of this aberrant E Coli strain

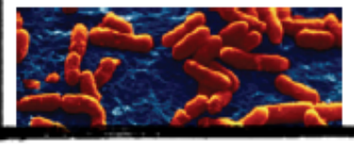
NHS choices

Your health, your choices

The rise of drug-resistant E. coli

Behind the Headlines
Brought to you by the NHS Knowledge Service

Tuesday February 19 2008



"if you reproduced every 20 minutes, you would get smart quickly, too"

The NEW ENGLAND JOURNAL of MEDICINE

NDM-1 — A Cause for Worldwide Concern

Robert C. Moellering, Jr., M.D.

n engl j med 363;25 nejm.org december 16, 2010

Antibiotic exposure and resistance development in *Pseudomonas aeruginosa* and *Enterobacter* species in intensive care units

Crit Care Med 2011; 39:000 – 000

Low exposure to antibiotics enables development of resistance

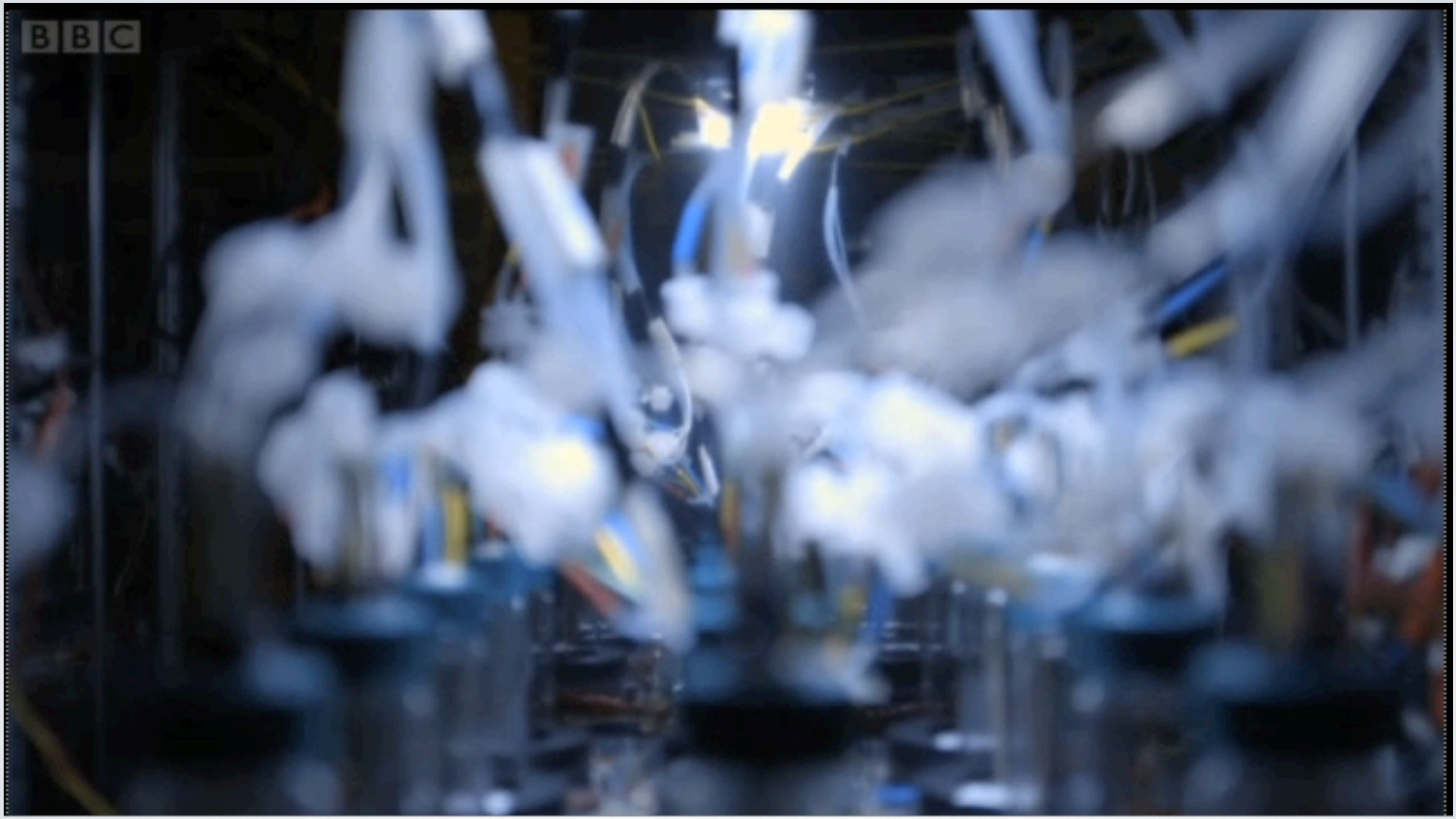
Antibiotic resistance—What's dosing got to do with it?

Jason A. Roberts, B Pharm (Hons); Peter Kruger, MBBS, FJFICM; David L. Paterson, MBBS, FRACP, PhD; Jeffrey Lipman, MBBCh, FJFICM, MD

Objective: This review seeks to identify original research articles that link antibiotic dosing and the development of antibiotic resistance for different antibiotic classes. Using this data, we tributing to the increasing rate of antibiotic resistance. Fluoroquinolones have widely been researched and publications on other antibiotic classes are emerging. Developing dosing regi-

Crit Care Med 2008; 36: 2433-2440

HOW TO "CREATE" RESISTANT ORGANISMS



Horizon BBC 2; 2012

INTRODUCTION

- Pathophysiological changes that occur in critically ill patients
- Effect these changes have on the pharmacokinetic behaviour of antibiotics
- Pharmacodynamic effect of commonly used antibiotics
- Identify things we do well and where gaps lie in our practice

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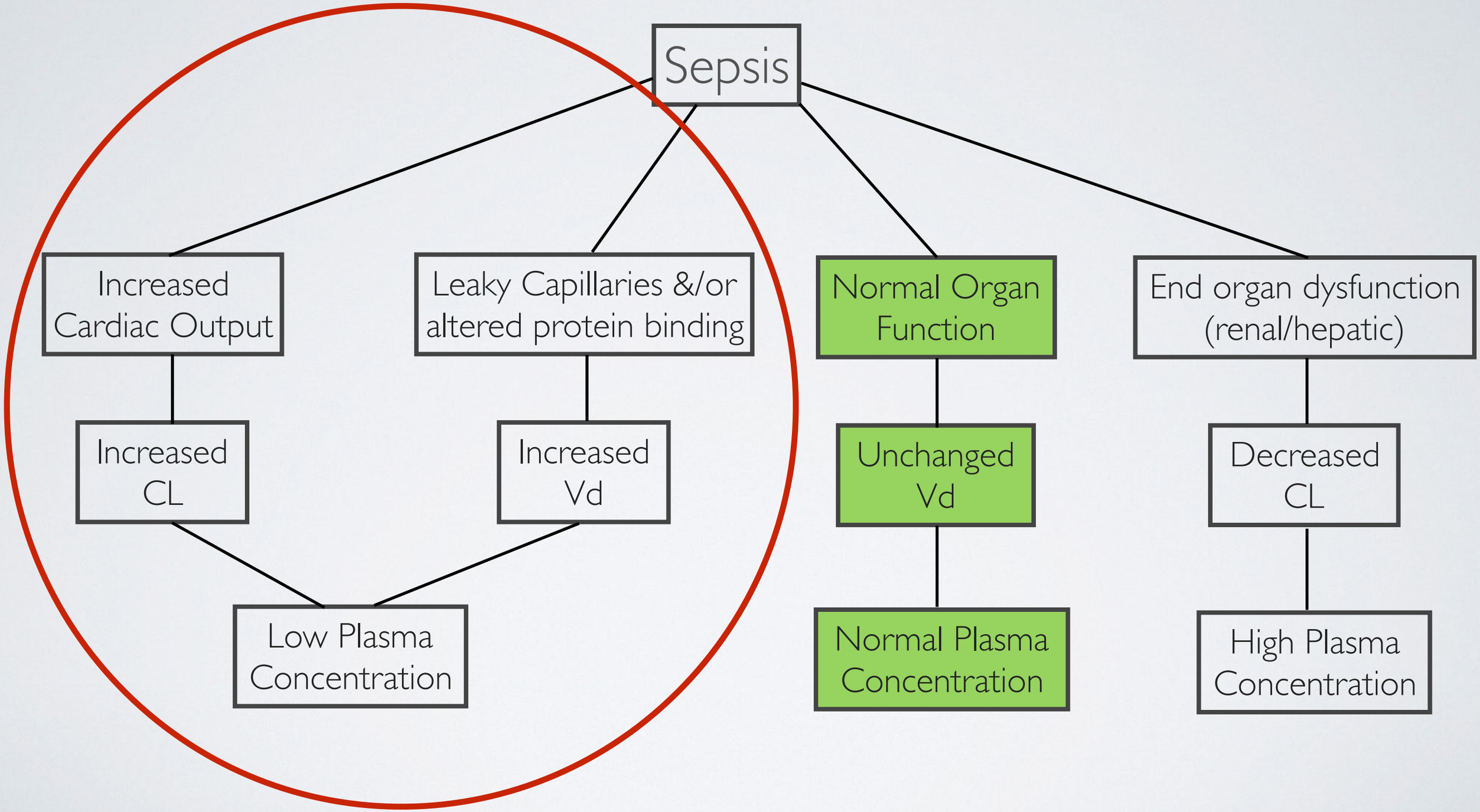
PATHOPHYSIOLOGICAL CHANGES THAT OCCUR DURING SEPSIS



Crit Care Med 2009; 37: 840-851

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Most dosage schemes were tested in **healthy** individuals and **not** on of **ICU** patients

	Result	Abx
Inotropes	**To be explored further.....**	
Fluid resuscitation		
Vessel leakage		
Low albumin		
AKI		
More resistant pathogens		

Crit Care 2009; 13:214

PHARMACOKINETIC FORMULAE

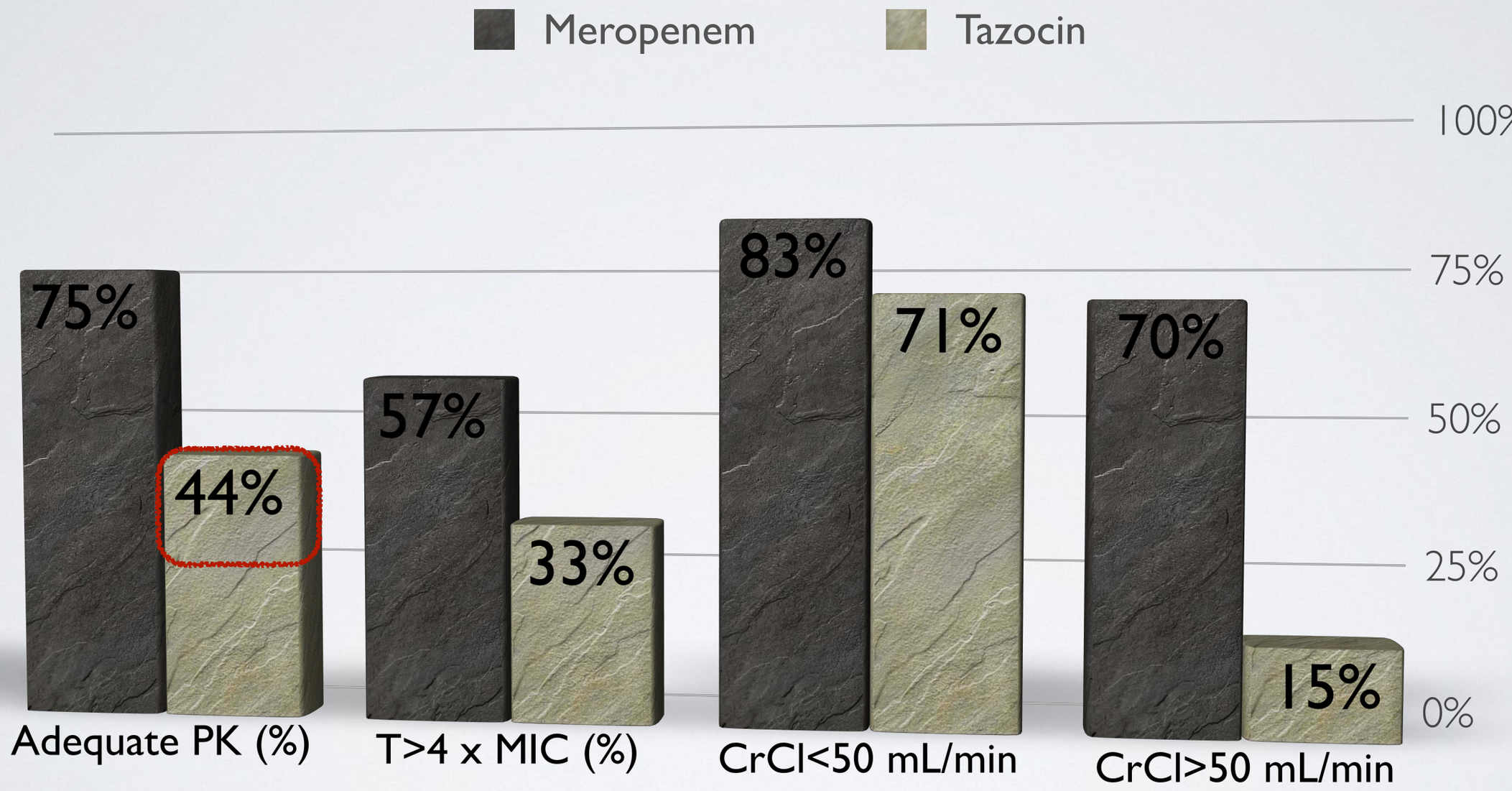
- Loading dose = Vd x Cp

NB: Renal function plays no role in the calculation of LD

- Antibiotic half-life (t1/2) = (0.693 x Vd)/CL

Increased drug CL is likely to reduce t1/2
Increased Vd is likely to increase t1/2

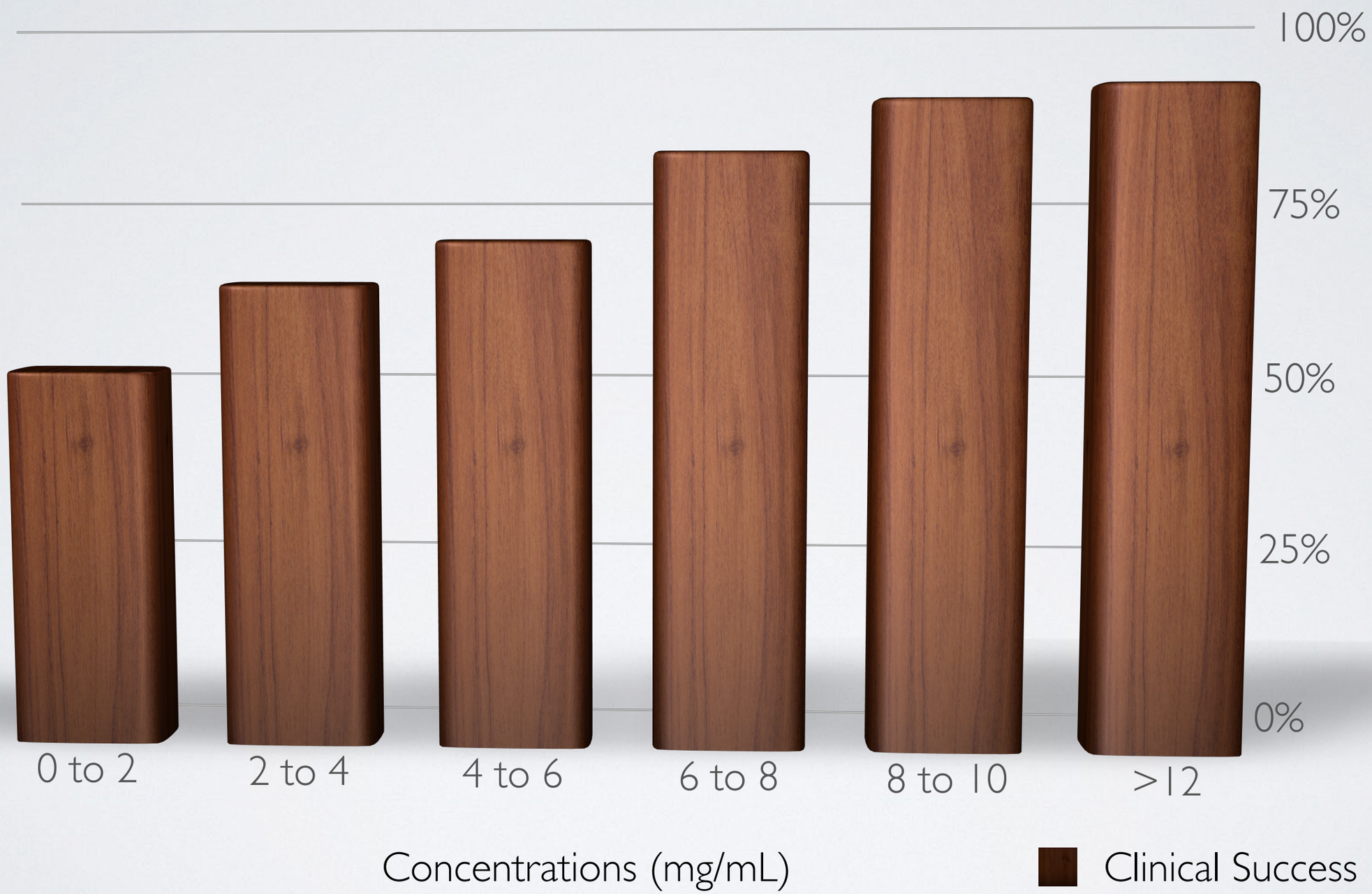
INSUFFICIENT ANTIBIOTIC CONCENTRATIONS IN THE EARLY PHASE OF SEPSIS



Adequate = % of time the serum drug concentration > 4 X MIC of Pseudomonas

Taccone et al Critical Care 2010

Aminoglycosides
relationship of **clinical success** and C_{max}/MIC ratio



Moore et al JID 1987, 155,93

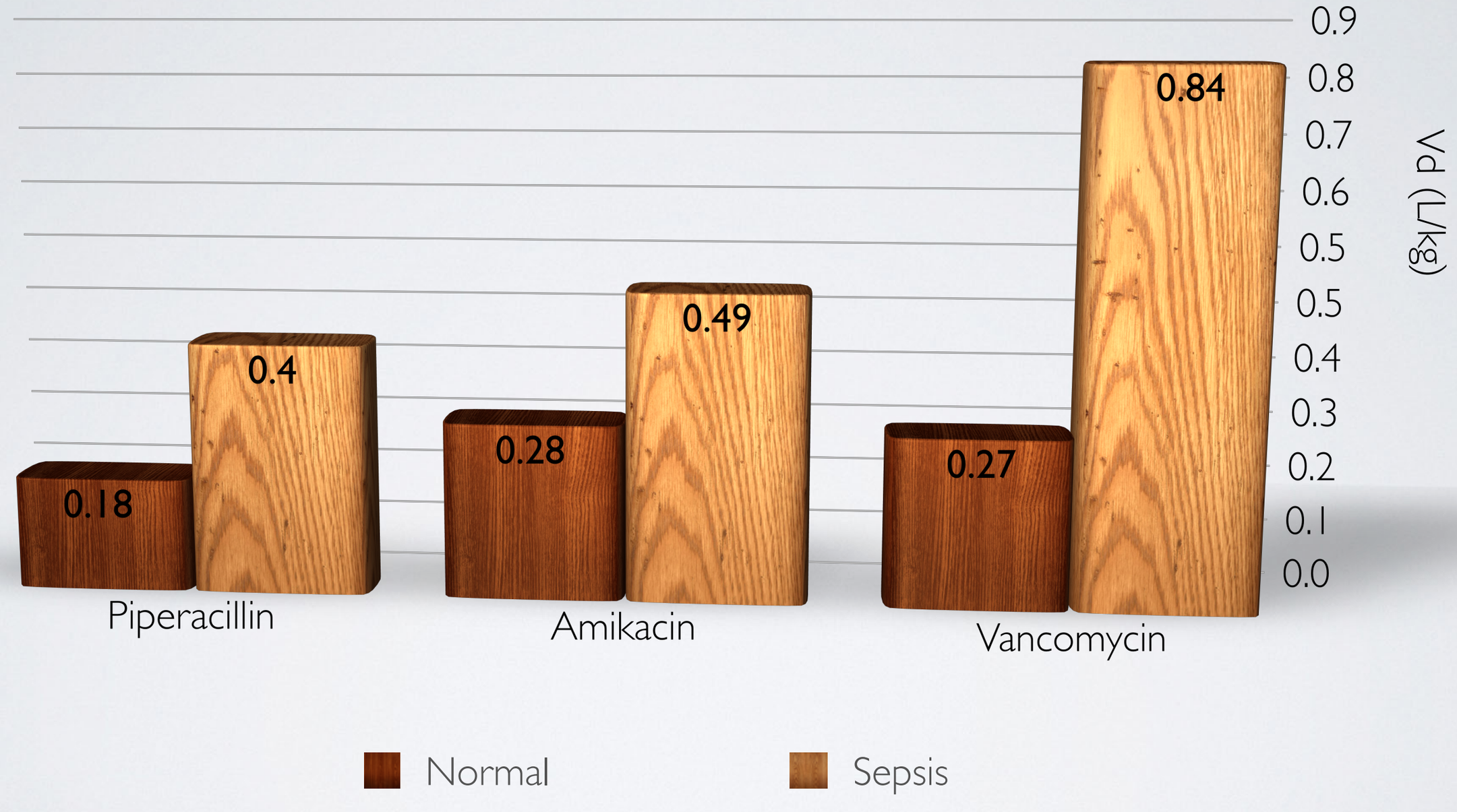
VOLUME OF DISTRIBUTION (VD)

- Capillary leak syndrome results in fluid shift from the intravascular compartment to the interstitial space

- Increases the Vd of **hydrophilic** drugs ⇒
  Decreases their plasma drug concentration

- **Lipophilic** drugs typically have a large Vd because of their partitioning into adipose tissue and as such the increased Vd that results from third spacing is likely to cause insignificant increases in drug Vd

Increased Vd in Sepsis



Roberts, Int J Antimicrob Agents 2009
Galvez, Int J Antimicrob Agents 2011

INTERRELATIONSHIP OF HYDROPHILICITY AND LIPOPHILICITY OF ABX MOLECULES

	Hydrophilic antibiotics	Lipophilic antibiotics
General PK	- Low Vd -Predominant renal CL -Low intracellular penetration	- High Vd -Predominant hepatic CL -Good intracellular
Altered PK	- Increased Vd -CL decreased or increased dependent on renal function	- Vd largely unchanged -CL decreased or increased dependent on hepatic function
Examples	- Beta lactams -Aminoglycosides -Glycopeptides -Linezolid -Colistin	- Macrolides -Clindamycins -Tigecycline

Crit Care Med 2009; 37: 840-851

	Result	Abs
Inotropes		
Fluid resuscitation		
Vessel leakage	Increased ‘third spacing'	More abx
Low albumin		
AKI		
More resistant pathogens		

AUGMENTED CREATININE CLEARANCE

In the context of antibacterial therapy, ARC has the potential to result in:

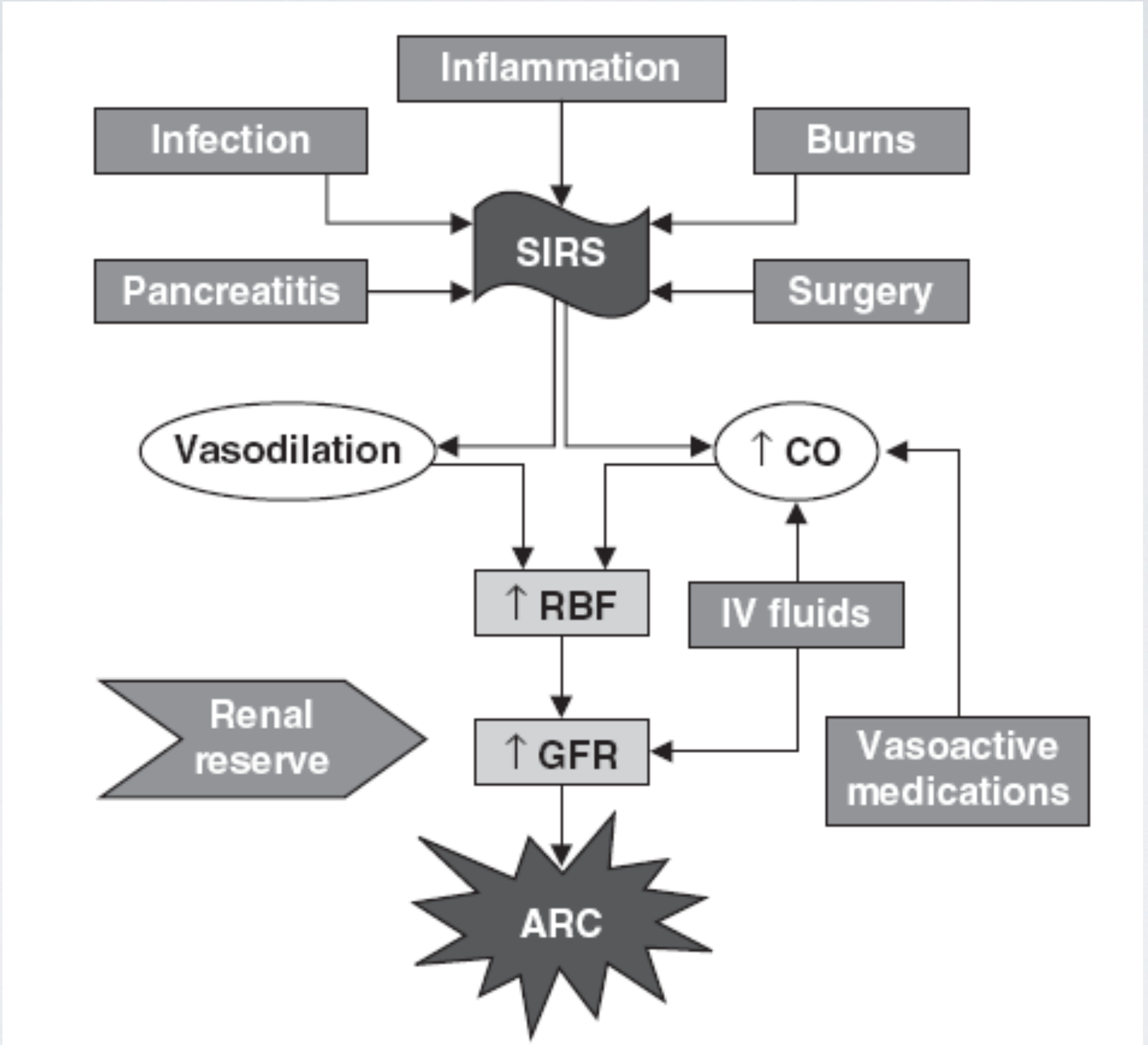
1. Sub-therapeutic dosing
2. Treatment failure
3. Selection of resistant micro-organisms

"Up to **30%** of ICU patients had **high** creatinine clearances!!"

Clin Pharmacokinet 2010; 49(1): 1-16

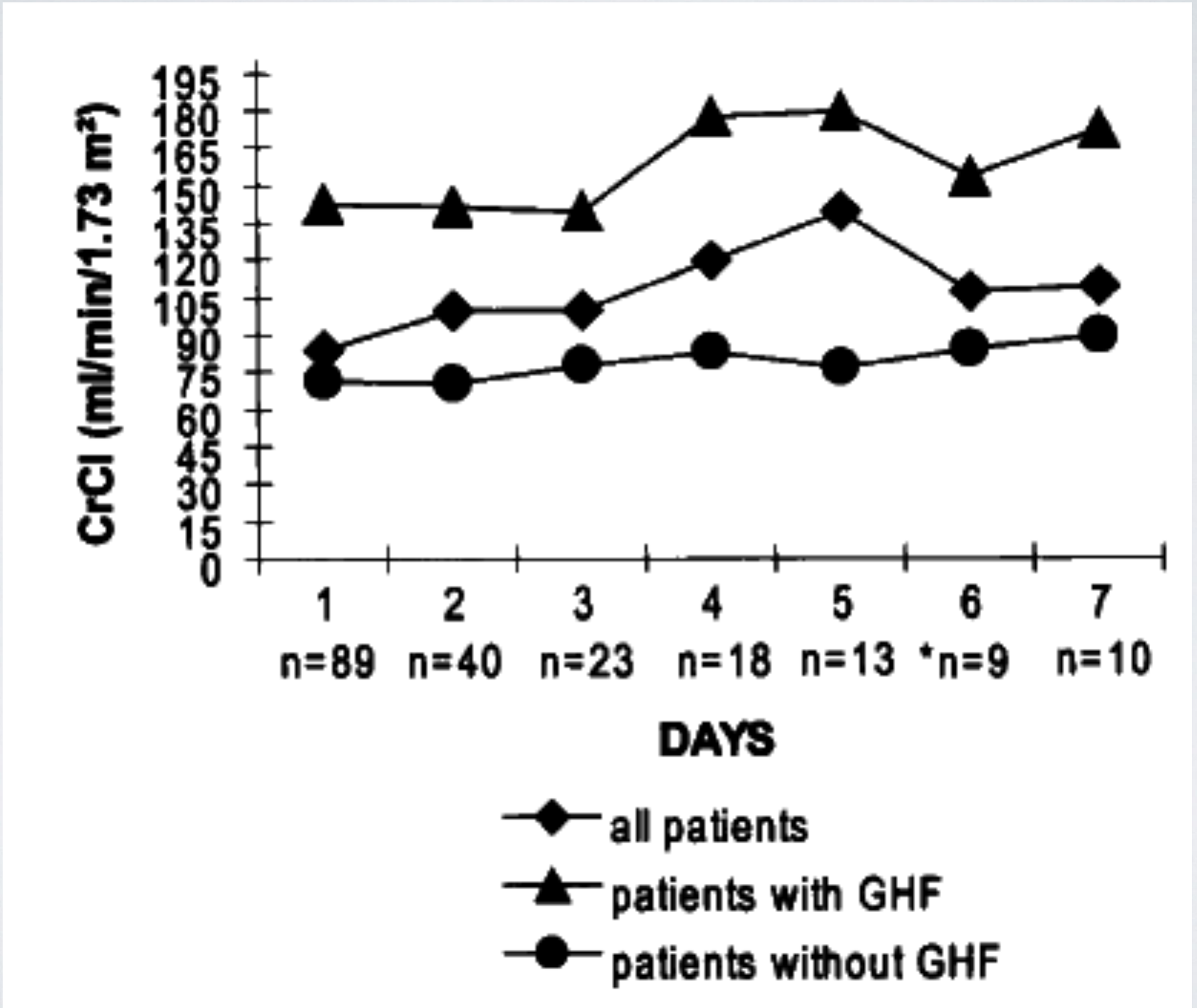
Anaesth Intensive Care 2008; 36:674-680

AUGMENTED CREATININE CLEARANCE



Clin Pharmacokinet 2010; 49(1): 1-16

GLOMERULAR HYPERFILTRATION



Anaesth Intensive Care 2008; 36: 674-680

	Result	Abs
Inotropes	Increased GFR	More abx
Fluid resuscitation	Increased VD	More abx
Vessel leakage	Increased 'third spacing'	More abx
Low albumin		
AKI		
More resistant pathogens		

HYPOALBUMINEMIA

- Protein binding may influence the Vd and CL of antibiotics

- E.g ceftriaxone - 95% bound to albumin in normal ward patients

- In hypoalbuminemia states this can result in a higher unbound concentration that has a 100% increased CL and 90% greater Vd

Anaesth Intensive Care 2008; 36: 674-680

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	Result	Abs
Inotropes	Increased GFR	More abx
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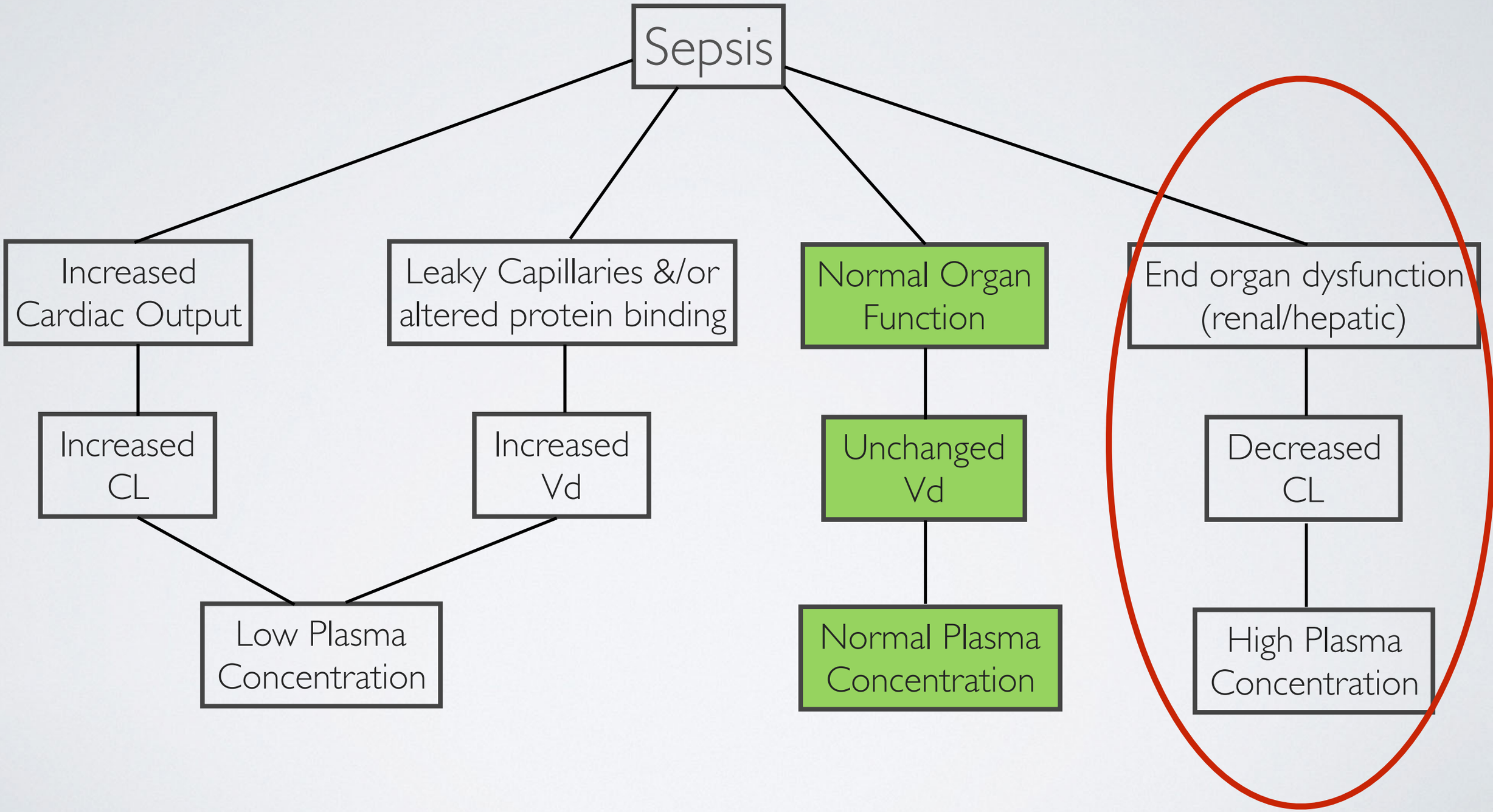
Low albumin	Increased free fraction	More abx
AKI		
More resistant pathogens		

DEVELOPMENT OF END ORGAN DYSFUNCTION

- Critical care patients do not present with homogenous pathology
- Myocardial depression can lead to a decrease in organ perfusion and failure of the microvascular circulation ⇒MOF

PATHOPHYSIOLOGICAL CHANGES THAT OCCUR DURING SEPSIS



Crit Care Med 2009; 37: 840-851

LIVER FAILURE

- Major site for drug elimination
- Hepatic metab ified into:

Compromised in liver failure

1. Phase 1 metabolism - e.g oxidation and methylation

2. Phase 2 metabolism e.g glucuronidation

RENAL FAILURE

- Elimination of hydrophilic antibiotics limited in renal failure
- Lipophylic antibiotics may produce renally eliminated metabolites

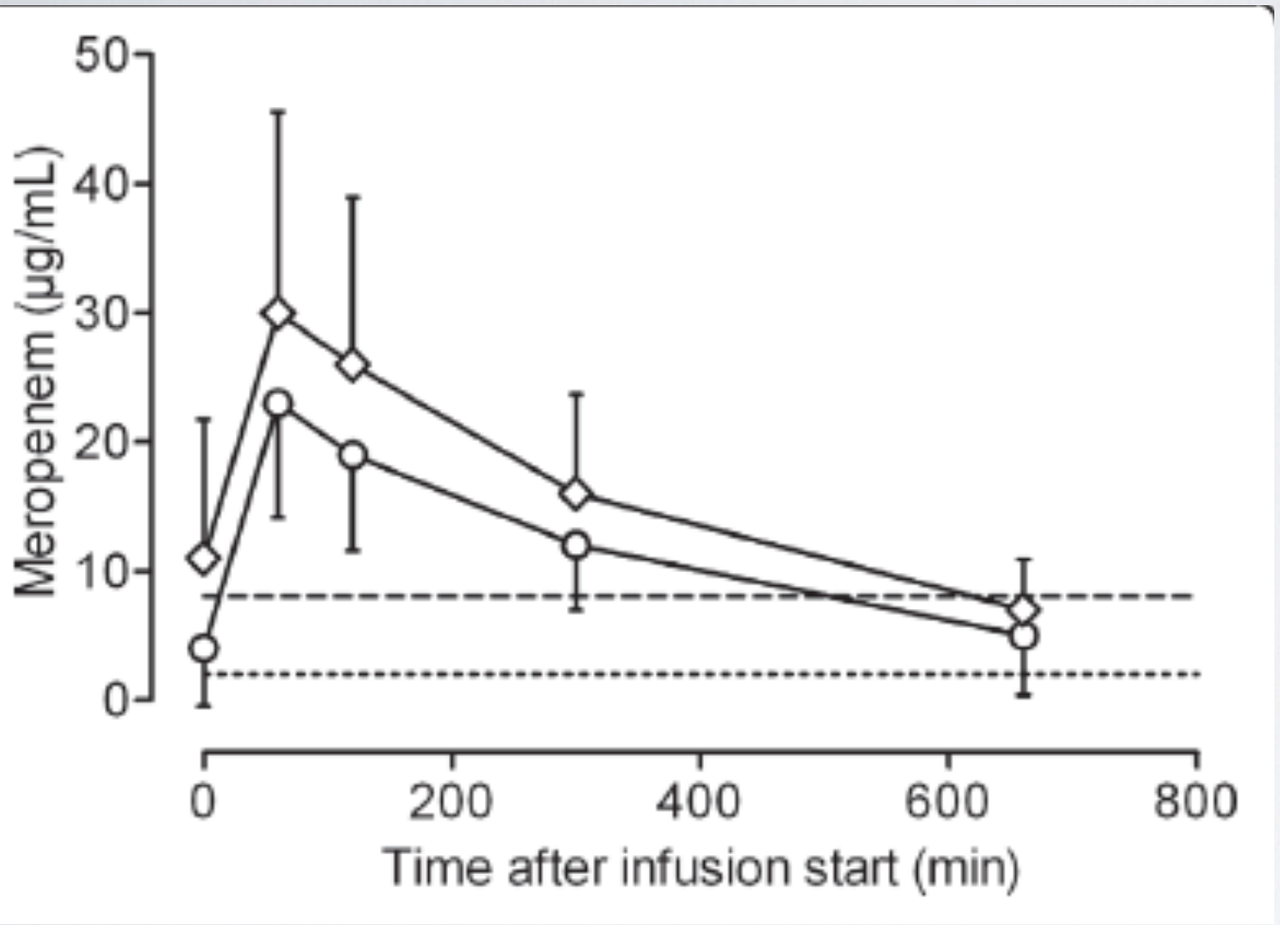
J Antimicrobial Chem 2011; 66 Suppl 2: ii25-ii31

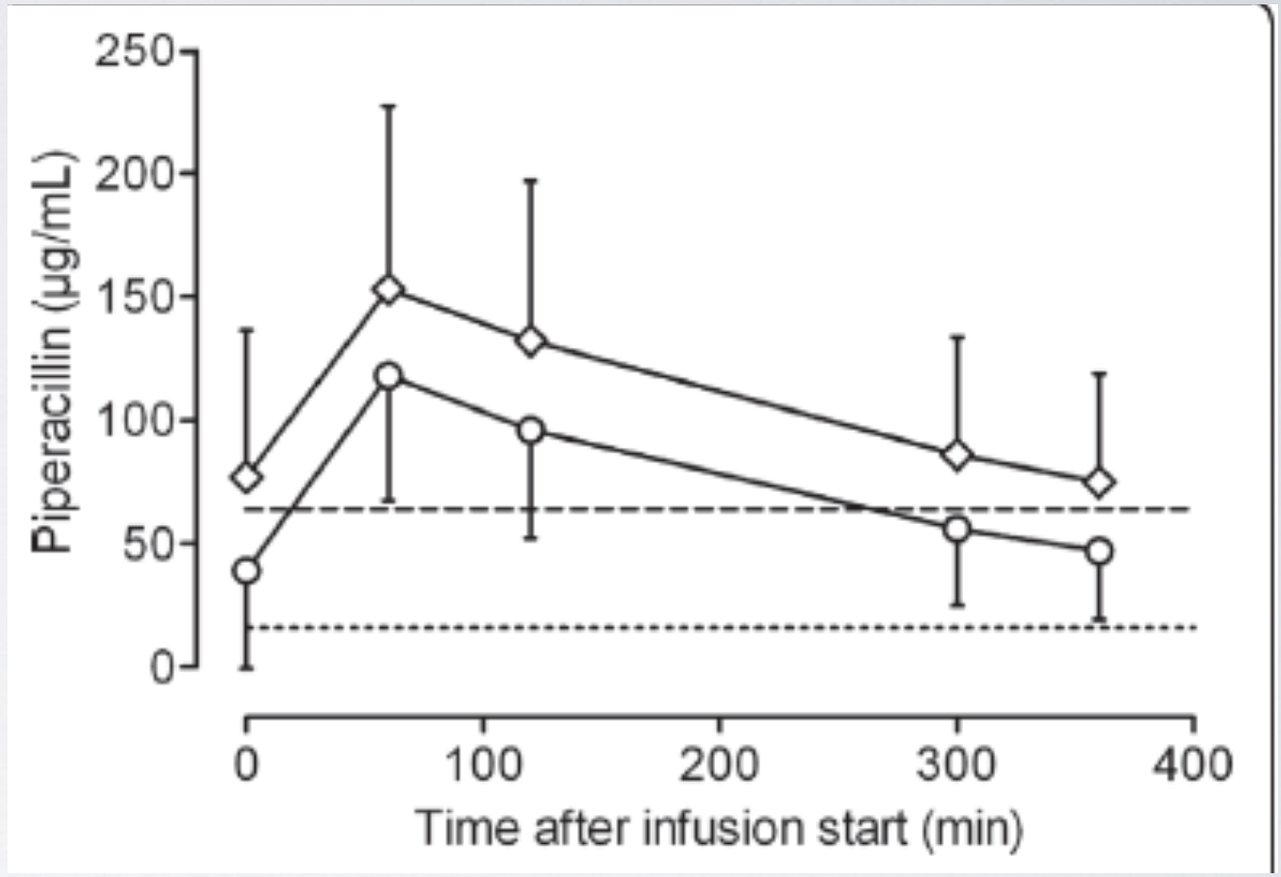
RENAL SUPPORT - CVVH

- Extracorporeal elimination only significant if **>35%**
- CVVH only replaces glomerular filtration
    - Do not use CrCl as basis of drug dosing in CVVH
- Factors that govern antibiotic removal
    - Renal excretion
    - Protein binding
    - Molecular weight
    - Membrane characteristics

J Antimicrobial Chem 2011; 66 Suppl 2: ii25-ii31

INADEQUATE DOSES OF BETA-LACTAMS IN CVVH





Critical Care 2011;15R137

	Result	Abs
Inotropes	Increased GFR	More abx
Fluid resuscitation	Increased VD	More abx
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Low albumin	Increased free fraction	More abx
AKI	**Decreased GFR**	**Less abx**
More resistant pathogens	PK/PD more important	More abx

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PLASMA CONCENTRATION (CP)

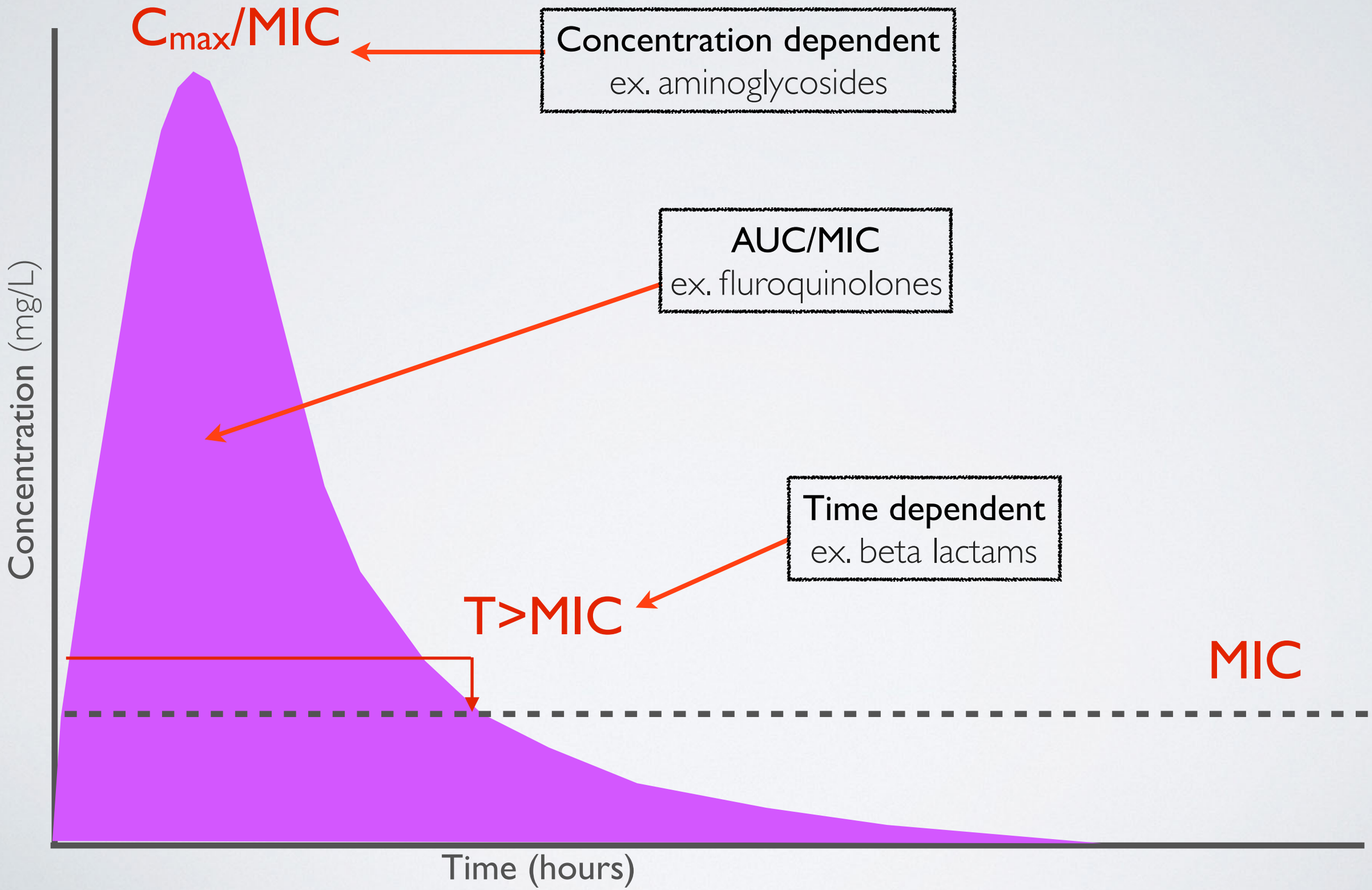
- The MICs of different antibiotics for susceptible bacteria vary greatly

- For **concentration dependent** antibiotics, a high initial dose is essential for maximum bactericidal effect

- For **time dependent** antibiotics the initial dose may not be crucial for pharmacokinetic effect

J Antimicrobial Chem 2011; 66 Suppl 2: ii25-ii31

PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS OF ANTIBIOTICS

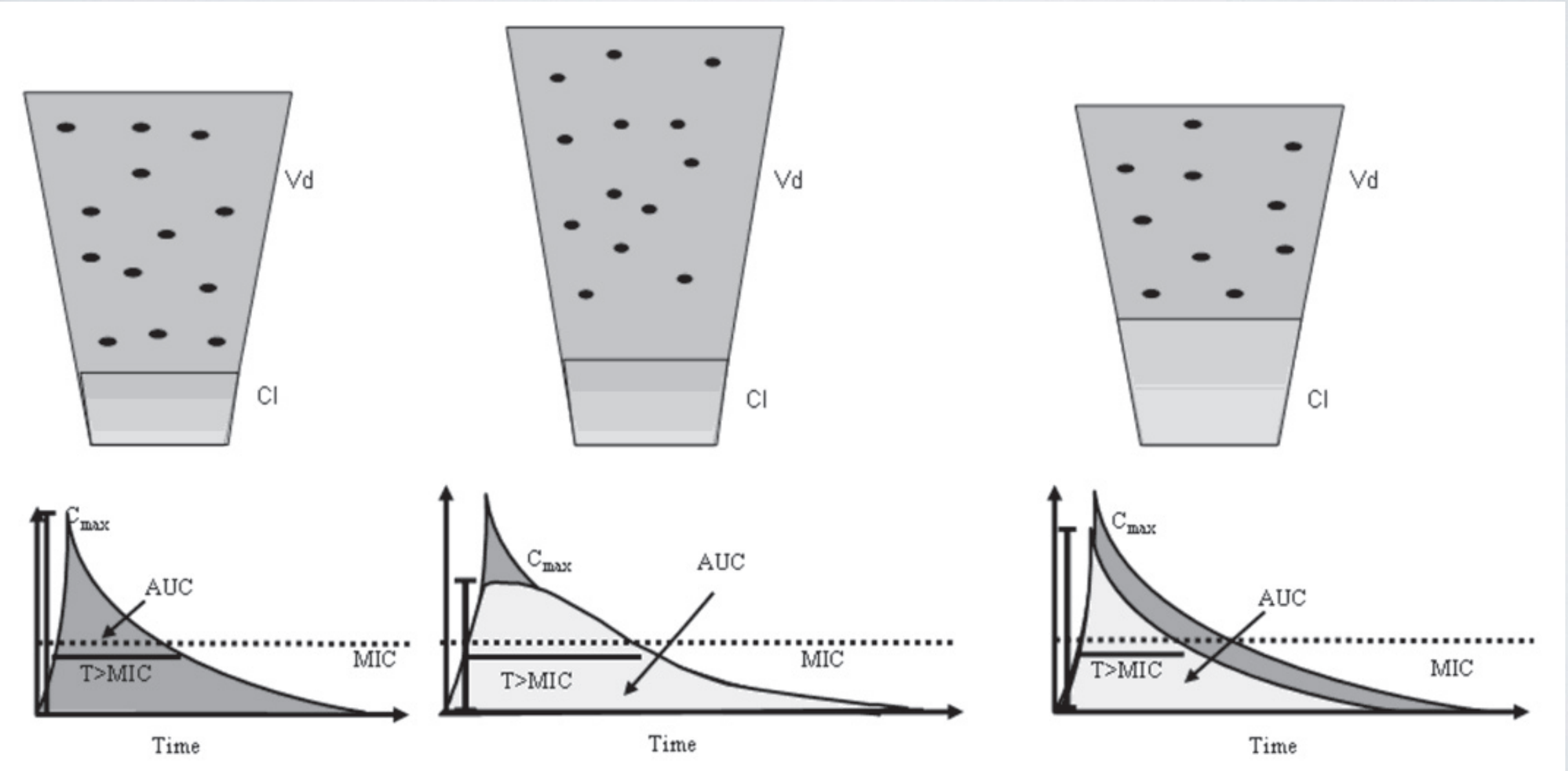


PHARMACODYNAMIC PROPERTIES THAT CORRELATE WITH EFFICACY OF SELECTED ANTIBIOTICS

Antibiotics	Beta-lactam Carbapenem Linezolid Erythromycin Clindamycin Clarithromycin	Aminoglycosides Metronidazole Fluoroquinolones Daptomycin	Fluoroquinolones Aminoglycosides Azithromycin Tetracyclines Glycopeptides Linezolid
PD kill characteristics	Time dependent	Concentration dependent	Concentration dependent with time dependent
Optimal PD parameter	T>MIC	C_{max}:MIC	AUC_{0-24}:MIC

Crit Care Med 2009; 37: 840-851

PHARMACOKINETICS CHANGES IN CRITICALLY ILL MAY ALTER BACTERIAL EXPOSURE



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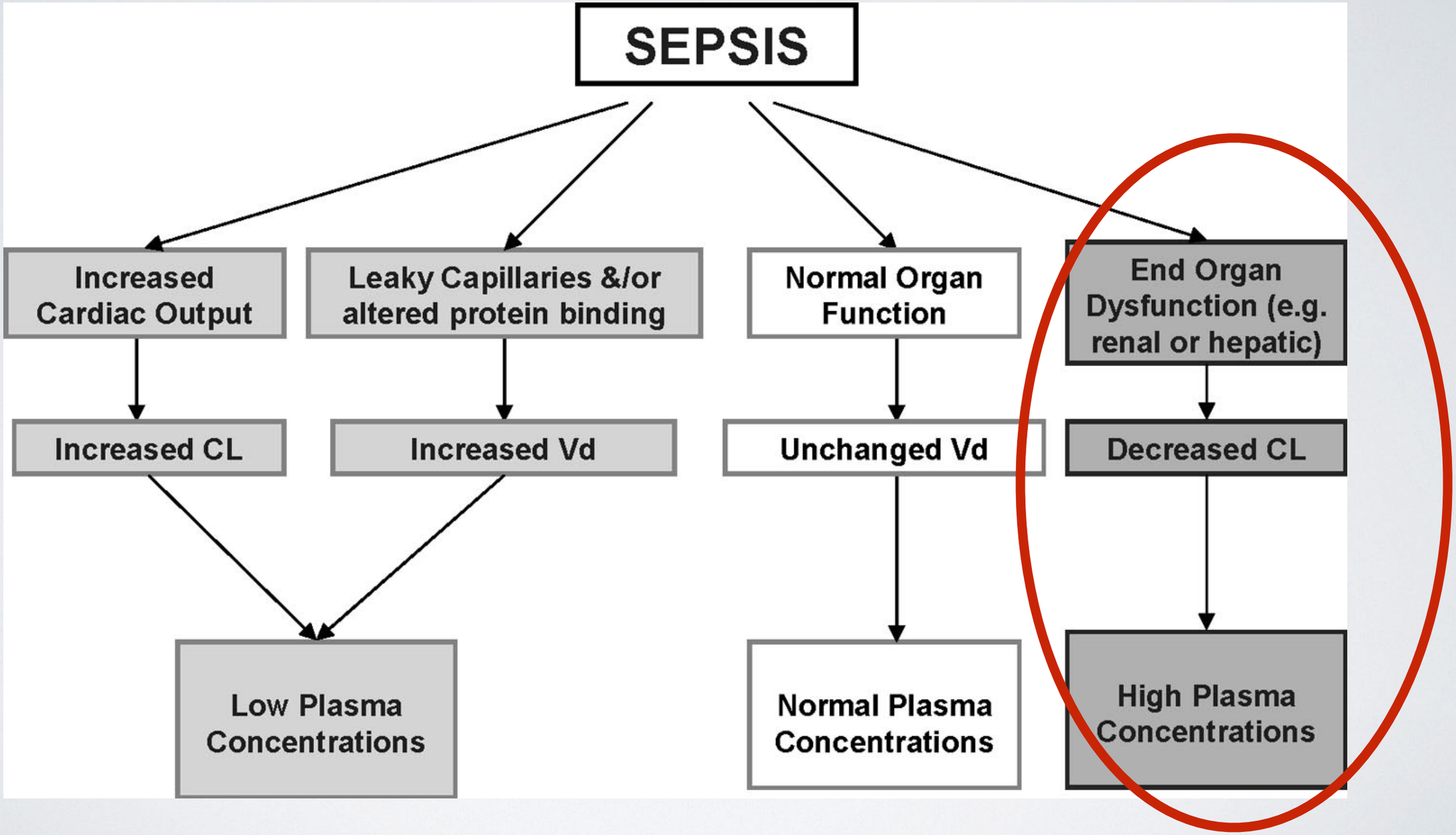

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PHARMACODYNAMIC PROPERTIES THAT CORRELATE WITH EFFICACY OF SELECTED ANTIBIOTICS

Antibiotics	Vd (L/kg)	Increased Vd with fluid shifts	Decreased Cmax with fluid shifts	Plasma T 1/2 (hrs)	Protein binding	Altered CL with critical illness	TDM required
Aminoglycosides	0.2-0.3 (~ ECF)	Yes	Yes	2-3	Low	Varies ~with renal function	Yes
Beta-lactams	Variable (~ ECF)	Yes	Yes	0.5 -2 (ceftriaxone 6-9 hrs)	Low (not ceftriaxone)	Varies ~with renal function	No
Carbapenems	Variable (~ ECF)	Yes	Yes	1 (ertapenem 4 hrs)	Low (not ertapenem)	Varies ~with renal function	No
Glycopeptides	0.2 - 1.6	Yes	Yes	4-6 vancomycin 80-160 teicoplanin	30-50% Vanc 90% teicpl	Varies ~with renal function. increased teic CL in low albumin	Yes

Crit Care Med 2009; 37: 840-851

INSUFFICIENT ANTIBIOTIC CONCENTRATIONS IN THE EARLY PHASE OF SEPSIS

Antibiotics	Meropenem	Tazocin
T>4 x MIC (%)	57	33
Adequate PK (%)	75	44
CrCl < 50 mL/min (%)	83	71
CrCl >50 mL/min (%)	70	15

Adequate = % of time the serum drug concentration > 4 X MIC of Pseudomonas

Taccone et al Critical Care 2010

AMINOGLYCOSIDES

- Concentration dependent
- Significant post antibiotic effect
- Maximal weight-based dosing consistently achieves adequate Cmax:MIC ratio
- Increased t1/2 in mechanical ventilation pts and burns pts
- Essential TDM due to adverse effects

Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock

Table 3: Differences in numbers of patients achieving optimal peak or high C_{min} concentrations

Regimen	Peak >64 µg/ml n (%)	C_{min} >5 µg/ml n (%)
15 mg/kg TBW	7 (9)	29 (39)
25 mg/kg TBW	50 (72)	39 (52)
30 mg/kg TBW	59 (79)	43 (58)
25 mg/kg IBW	35 (47)	39 (52)
25 mg/kg DW	42 (56)	39 (52)

Doses were calculated by using total body weight (TBW), ideal body weight (IBW), or IBW with correction factors (DW) for extreme body mass

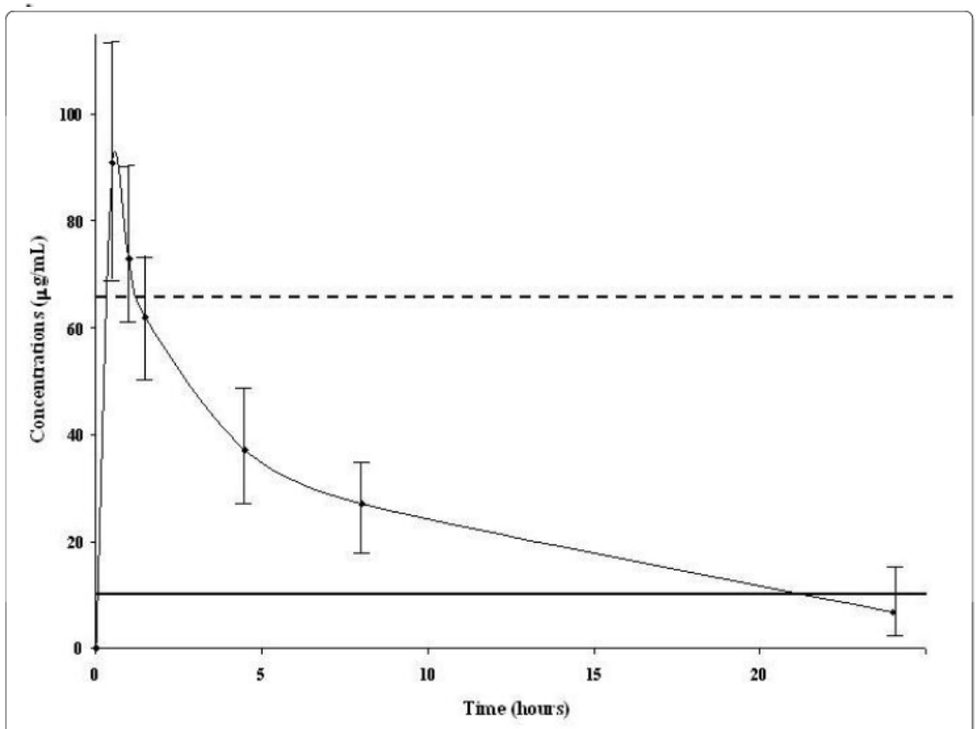


Figure 1 Pharmacokinetic profile of amikacin. Dashed line, peak of 64 µg/ml corresponding to 8 times the clinical breakpoint of the minimal inhibitory concentration (MIC = 8 µg/ml, solid line) for gram-negative bacteria.

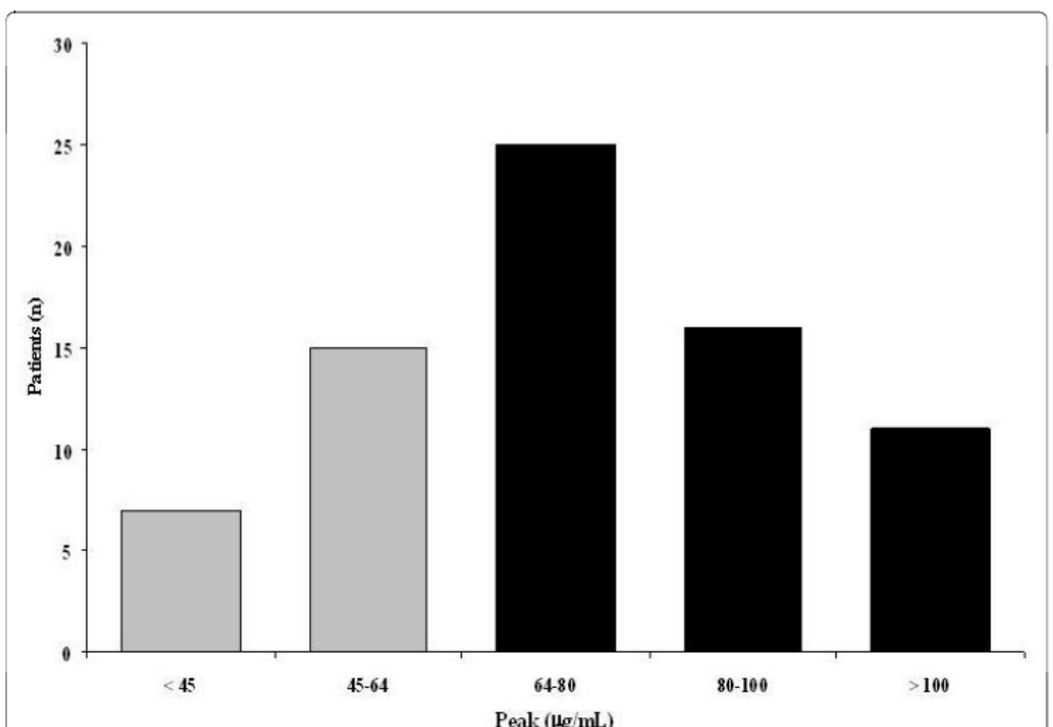
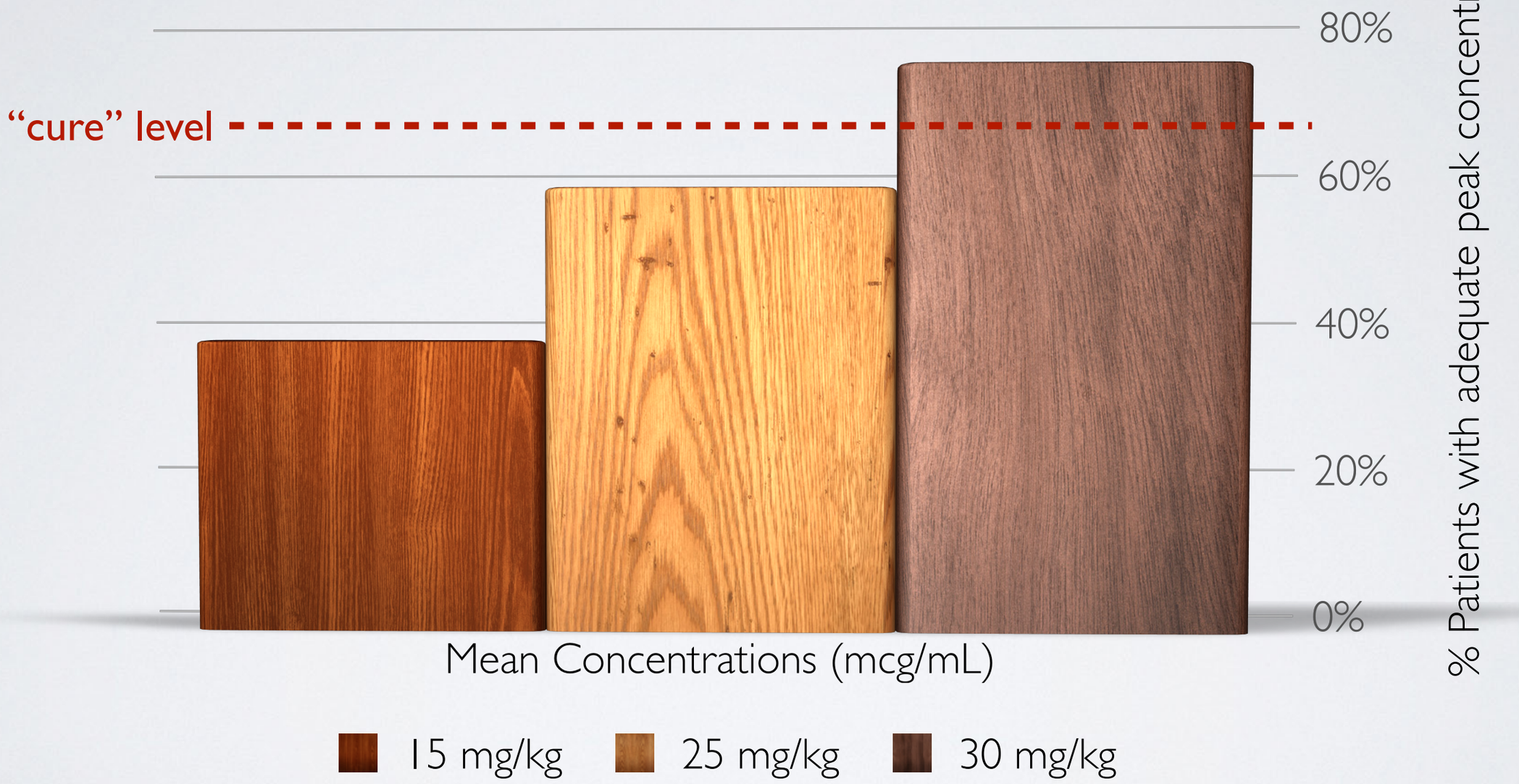


Figure 2 Distribution of peak concentrations. Black bars, peak >64 µg/ml; gray bars, peak <64 µg/ml.

Amikacin - Increased Doses

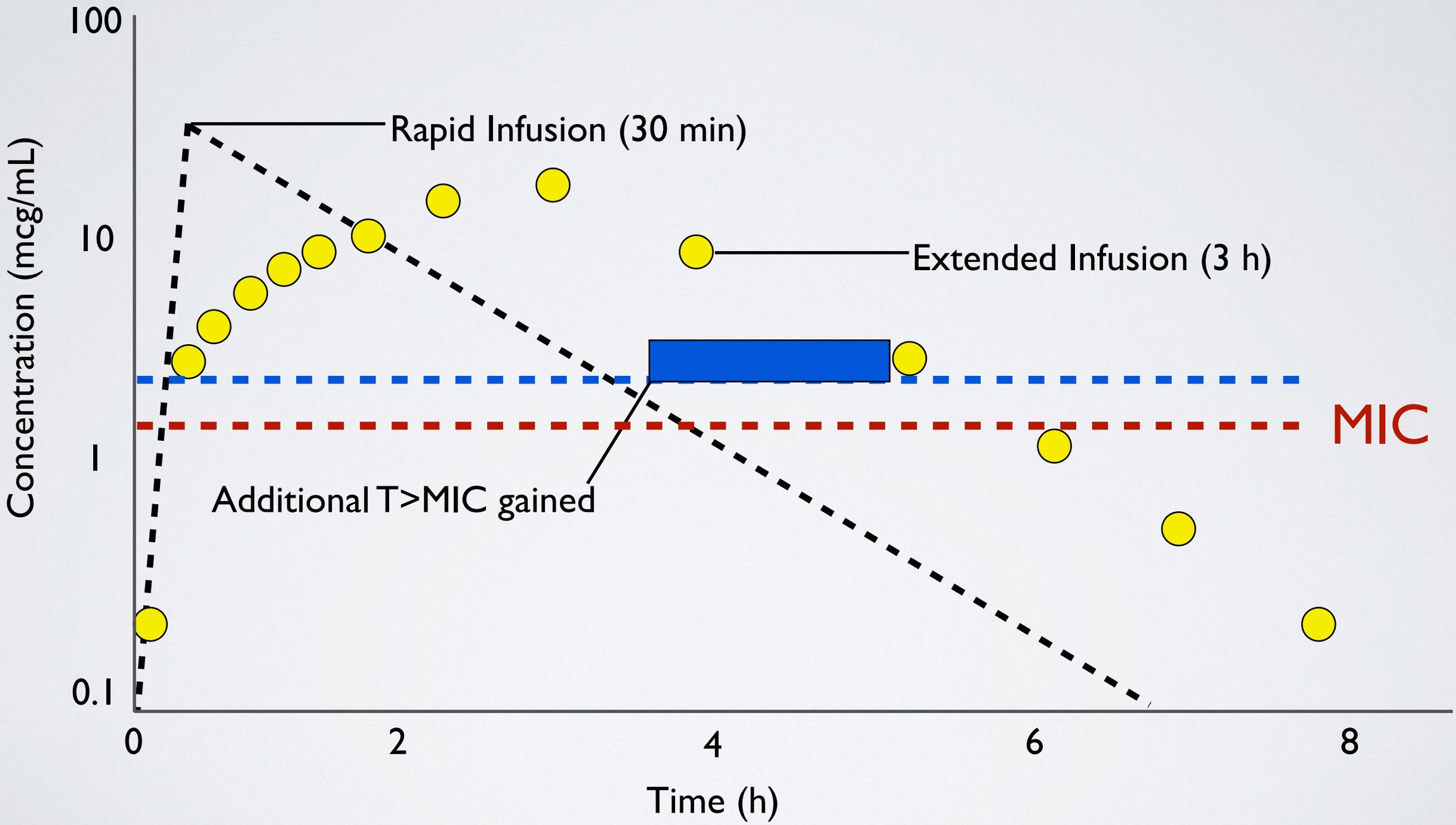


Galvez, Int J Antimicrob Agents 2011

BETA-LACTAMS

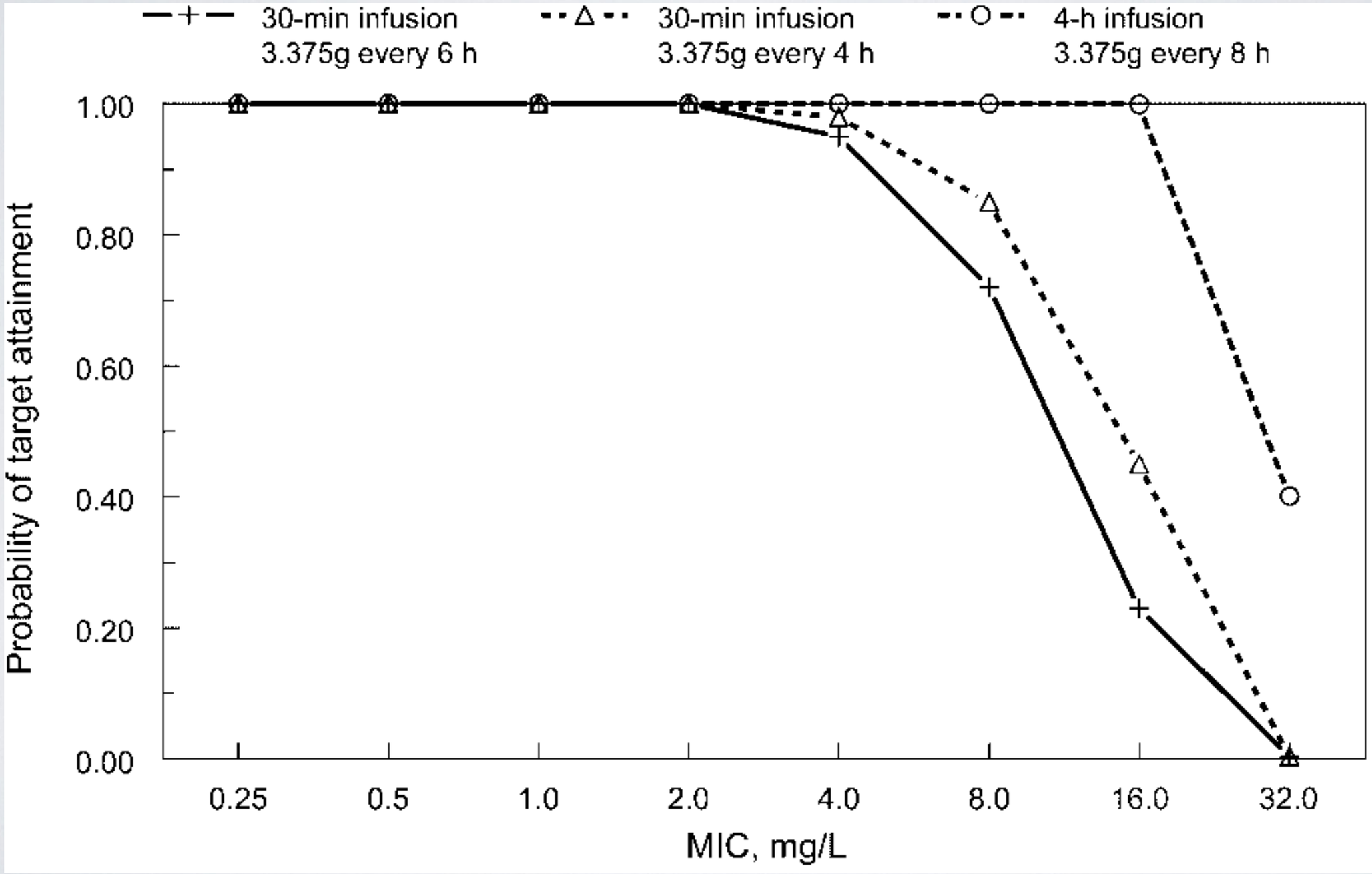
- Includes penicillins, cephalosporins, carbapenems
- Time dependent killing
- Serum concentration above MIC
- No significant post-antibiotic effect, except for carbapenems
- Slow continuous kill characteristic - related to T>MIC

Meropenem 500 mg administered as 3 hr infusion extends the time over the MIC vs 0.5 h infusion

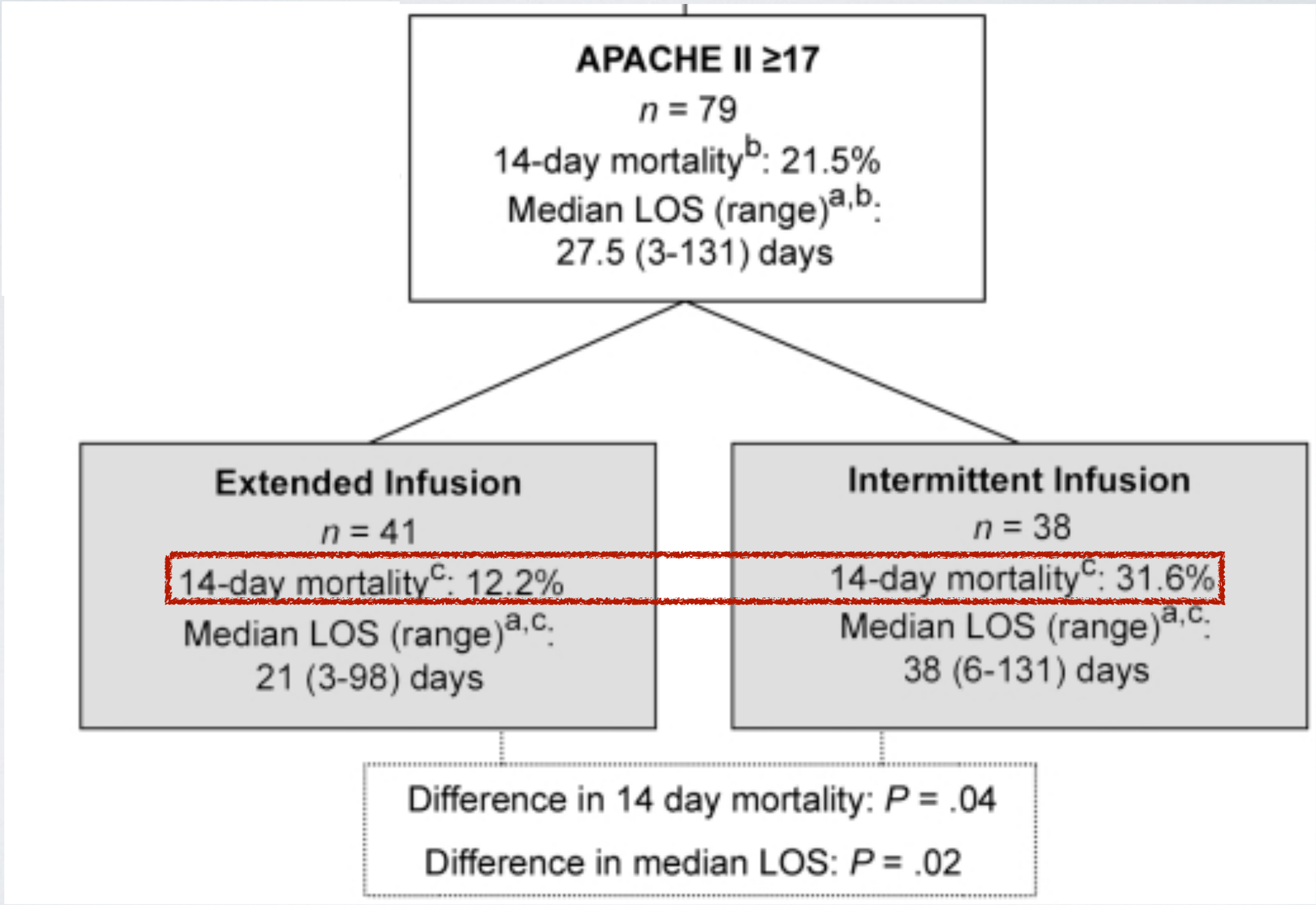


Dandeker et al. Pharmacotherapy 2003;23:988-991

Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy



Lodise et al, CID 2007; 44


APACHE II ≥17
n = 79
14-day mortality[b]: 21.5%
Median LOS (range)[a,b]:
27.5 (3-131) days
Extended Infusion
n = 41
14-day mortality[c]: 12.2%
Median LOS (range)[a,c]:
21 (3-98) days
Intermittent Infusion
n = 38
14-day mortality[c]: 31.6%
Median LOS (range)[a,c]:
38 (6-131) days
Difference in 14 day mortality: P = .04
Difference in median LOS: P = .02

LOTS OF WORK TO BE DONE

- For septic patients start treatment **early**
- Take **cultures** prior to antibiotics
- **De-escalation** of therapy
- **Individualised** dosing regimens
- ITU working group

RECAP

- PK of antibiotics different in critically ill
  - large Vd
  - may have increased GFR (~30%)
- Therapeutic monitoring of drug levels
  - adequate "cure" levels
  - avoid toxic levels
- Inadequate antibiotic levels causes resistance

???