XX Reunião Nacional do Núcleo de Medicina Interna dos Hospitais Distritais

Antibiotics

The When and the How

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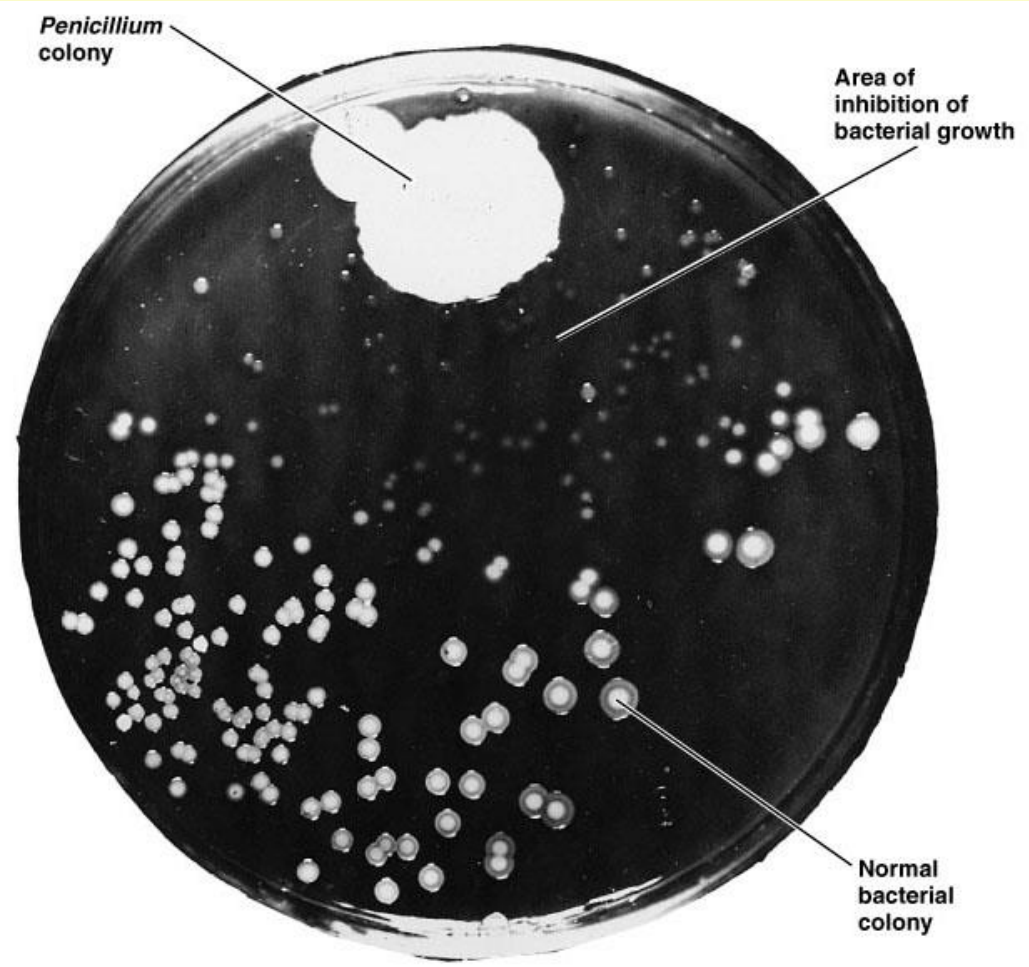
Vila Franca Xira Hospital

Antibiotics

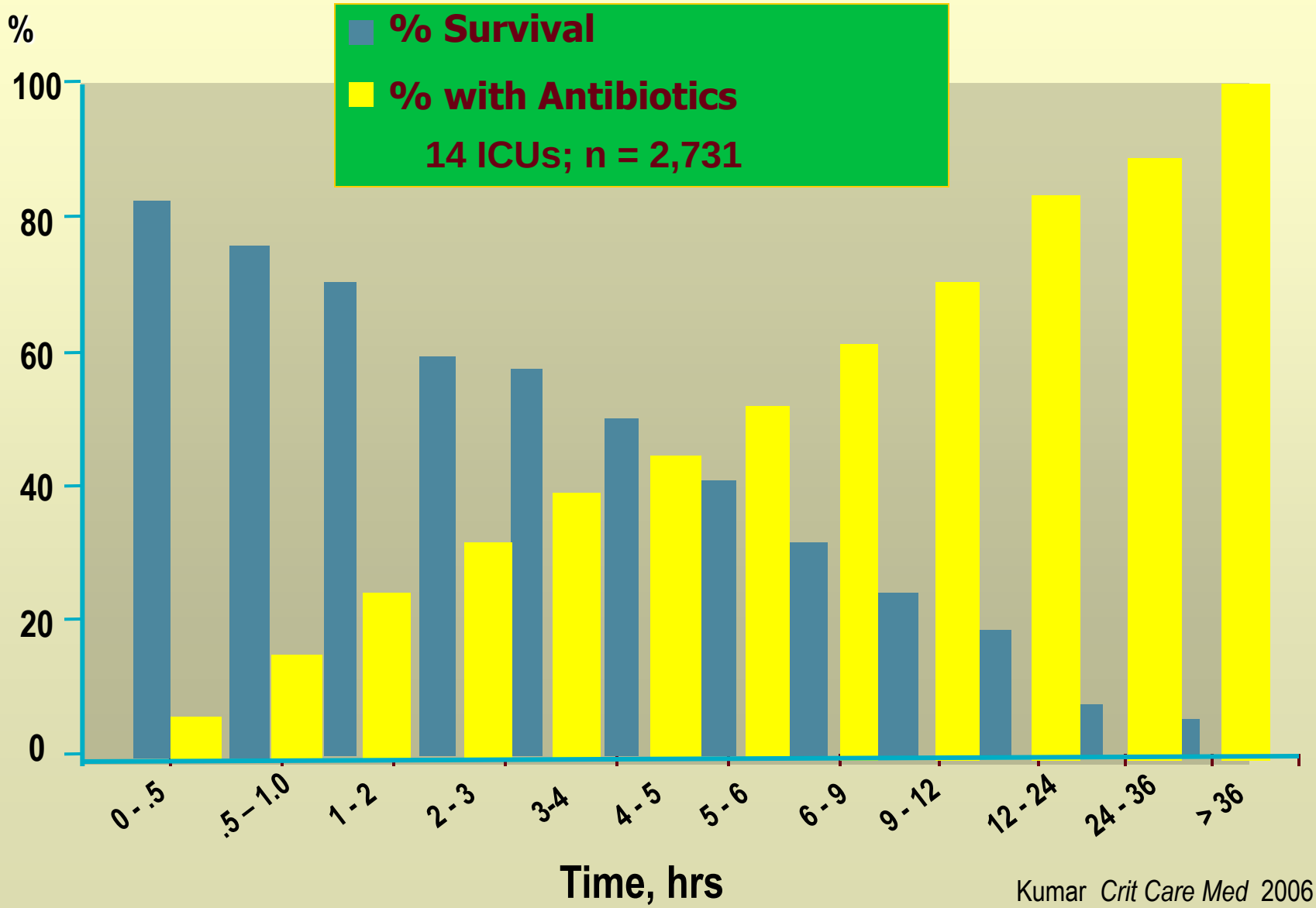
End of Sec. XIX – Arsfenamine synthesis by Paul Ehrlich

"Magic Bullets"

- **1928 – Fleming discovers penicillin, from a fungae, *Penicillium*.**
- **1940 – Howard Florey and Ernst Chain made first therapeutic study with penicillin.**

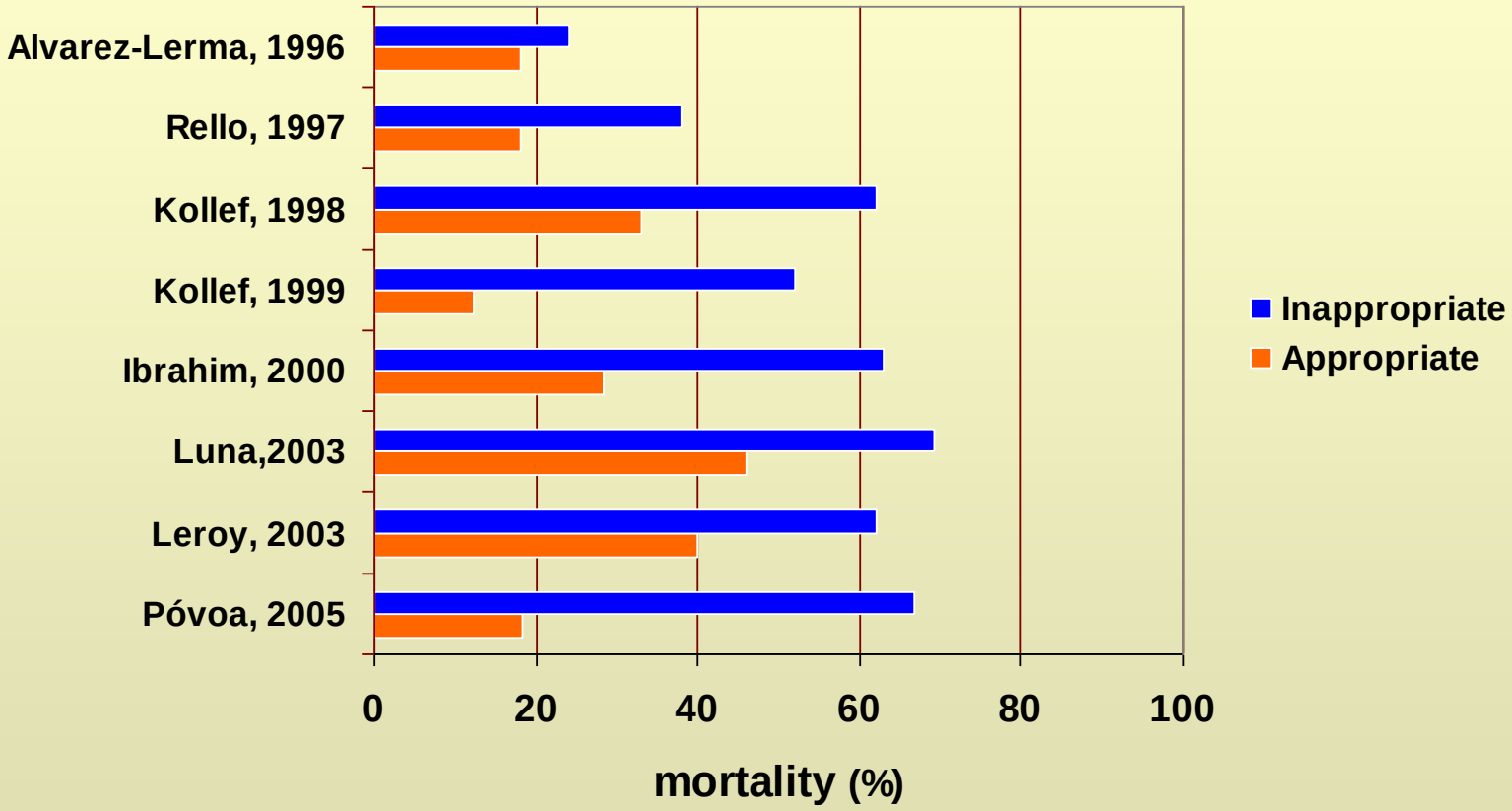


Time of antibiotics in patients with septic shock



Kumar *Crit Care Med* 2006

Initial Antibiotic therapy and Mortality

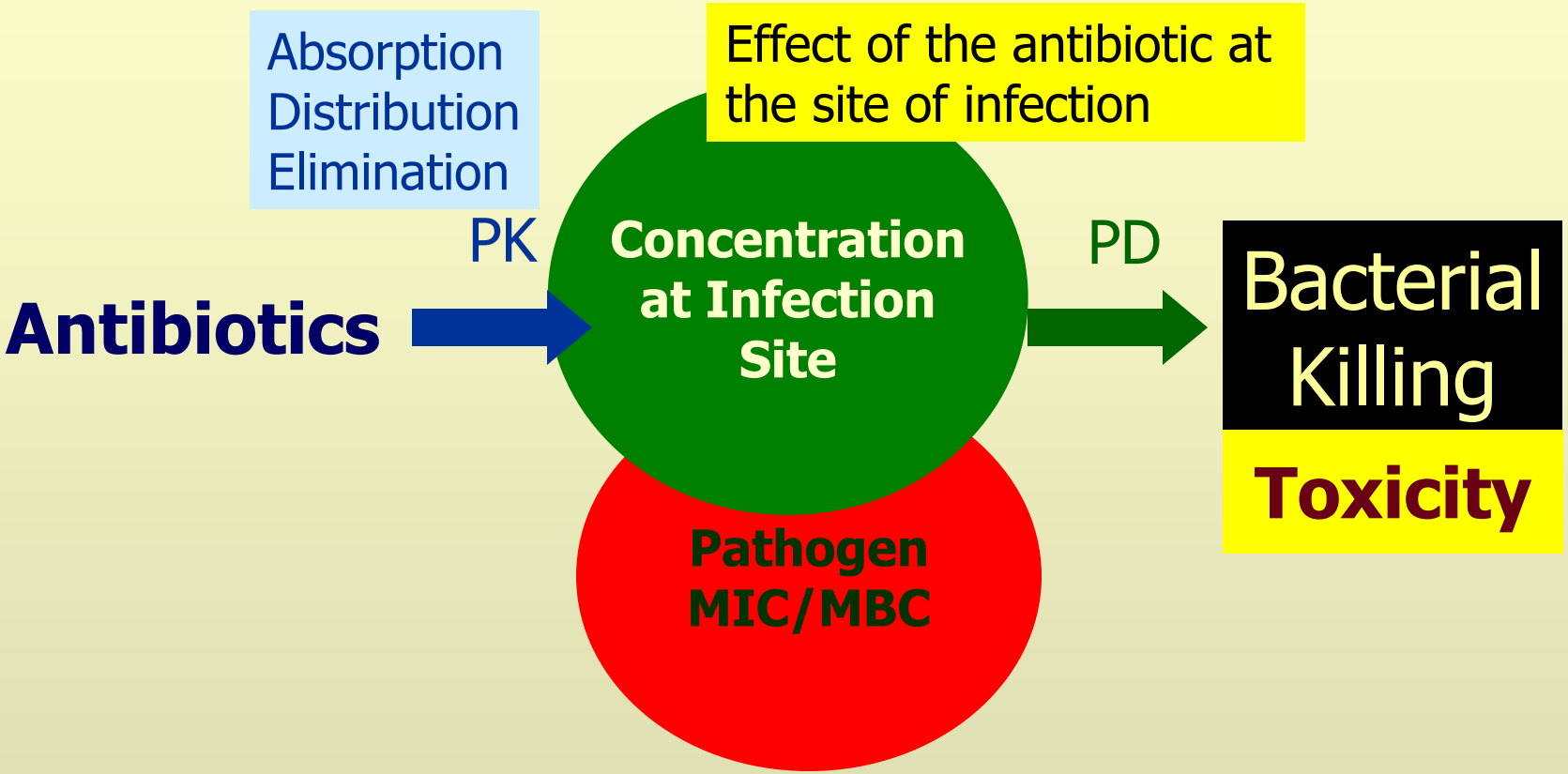


Alvarez-Lerma F. ICM 1996
Kollef MH, Chest. 1999
Leroy O ICM 2003

Rello J, AJRCCM 1997
Ibrahim EH Chest. 2000
Póvoa P ERJ 2005

Kollef MH. Chest. 1998
Luna CM, Chest. 1997

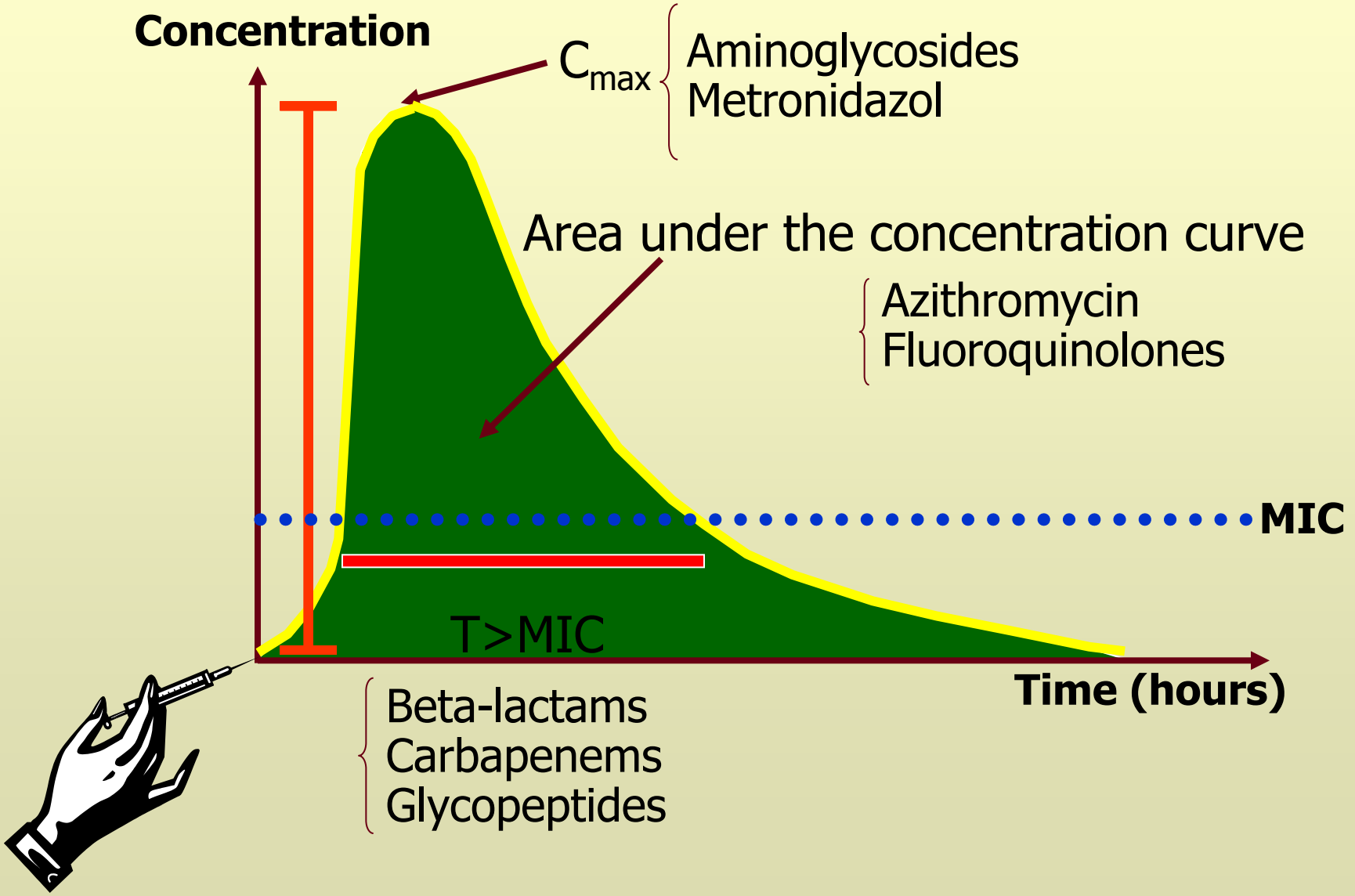
Antimicrobial therapy



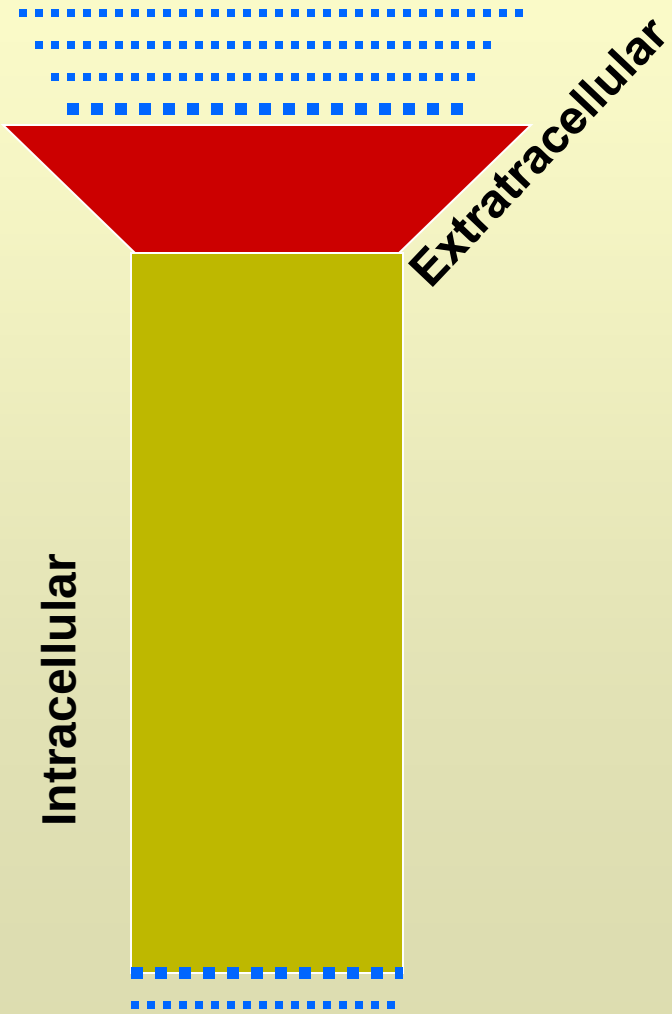
Dosing of antibiotics to maximize the exposure of antibiotics to bacteria

Craig WA - CID 1998; 26.1

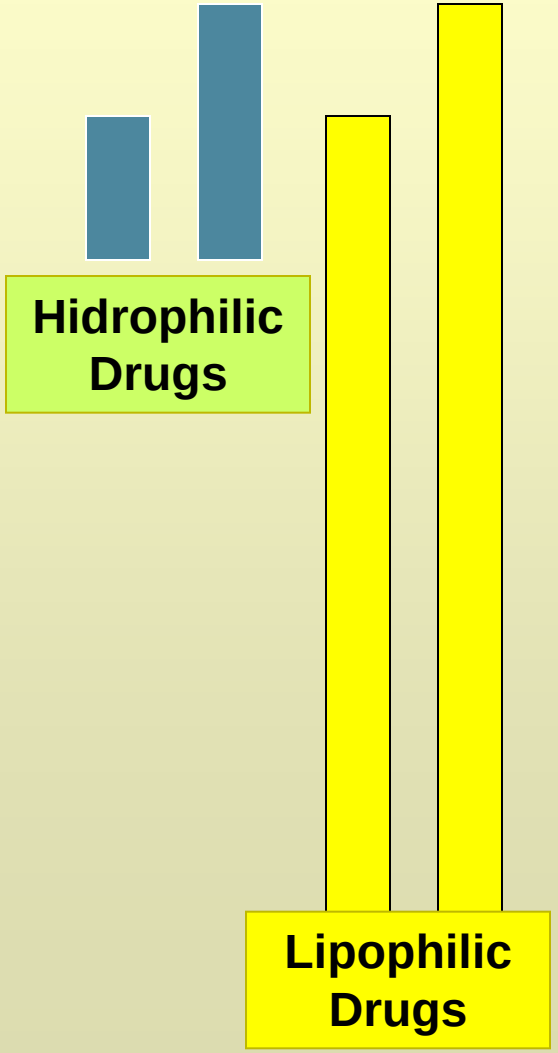
Patterns of Antimicrobial Activity



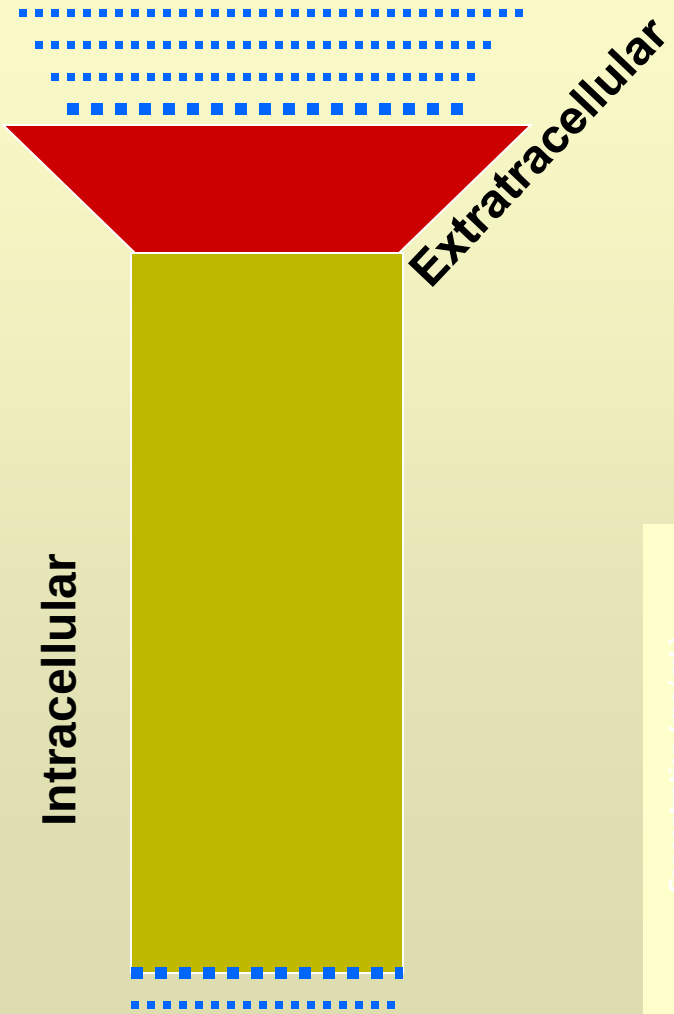
Volume of Distribution



Volume Resuscitation

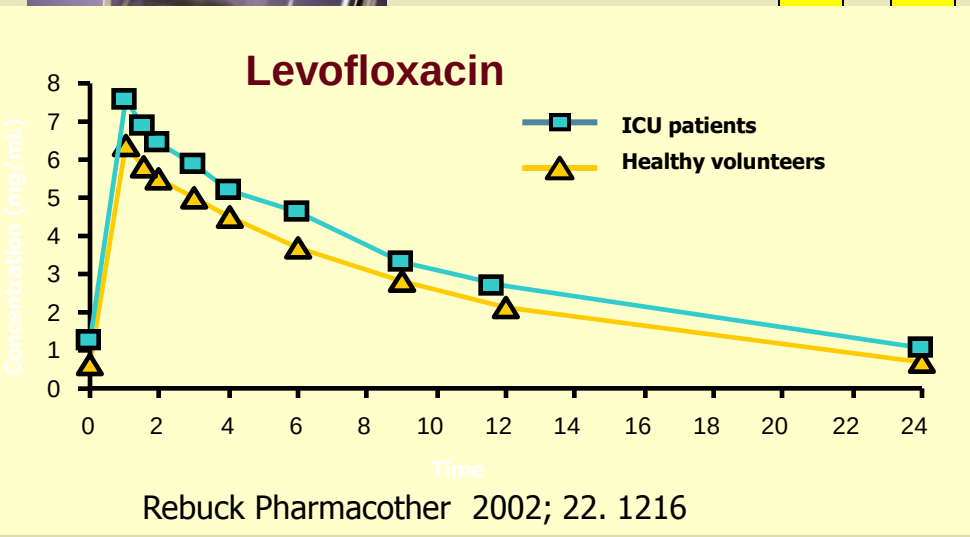


Volume of Distribution



Volume Resuscitation

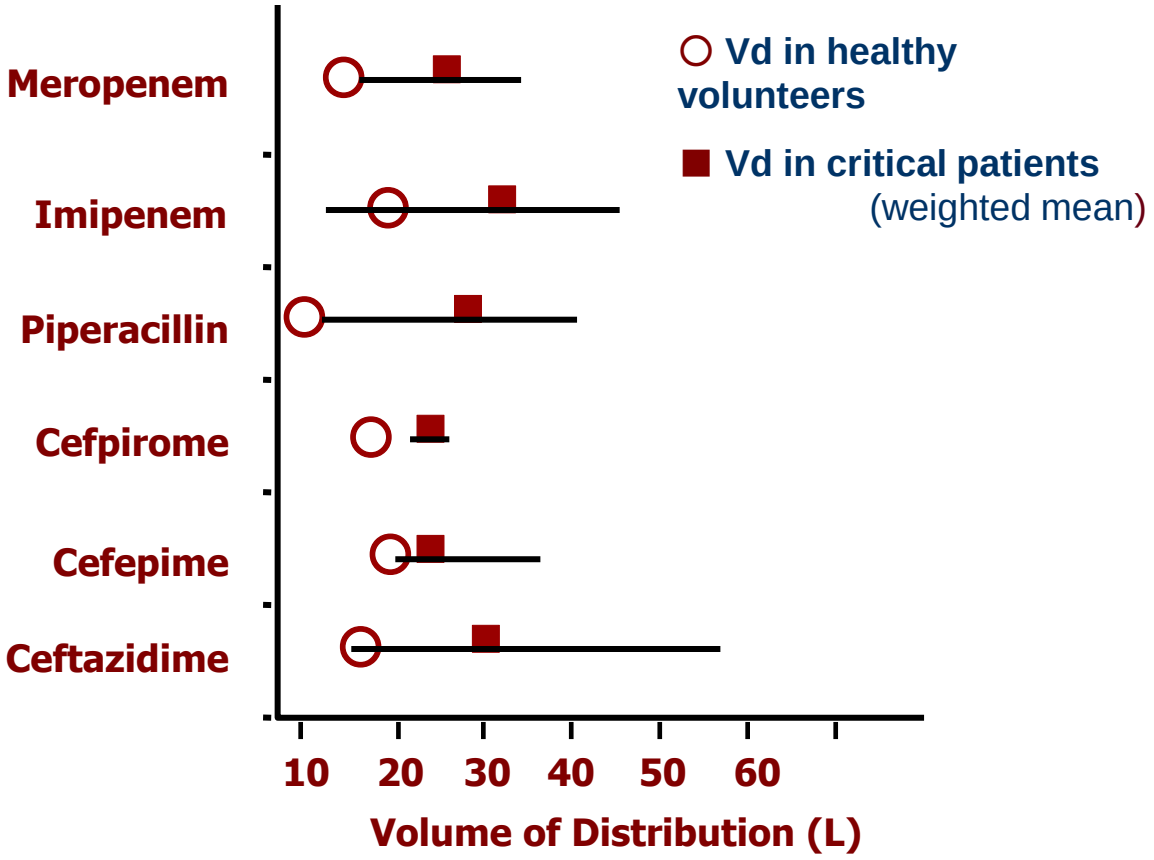
Gomez 1999; 43:1789



Rebuck Pharmacother 2002; 22. 1216

Volume of Distribution

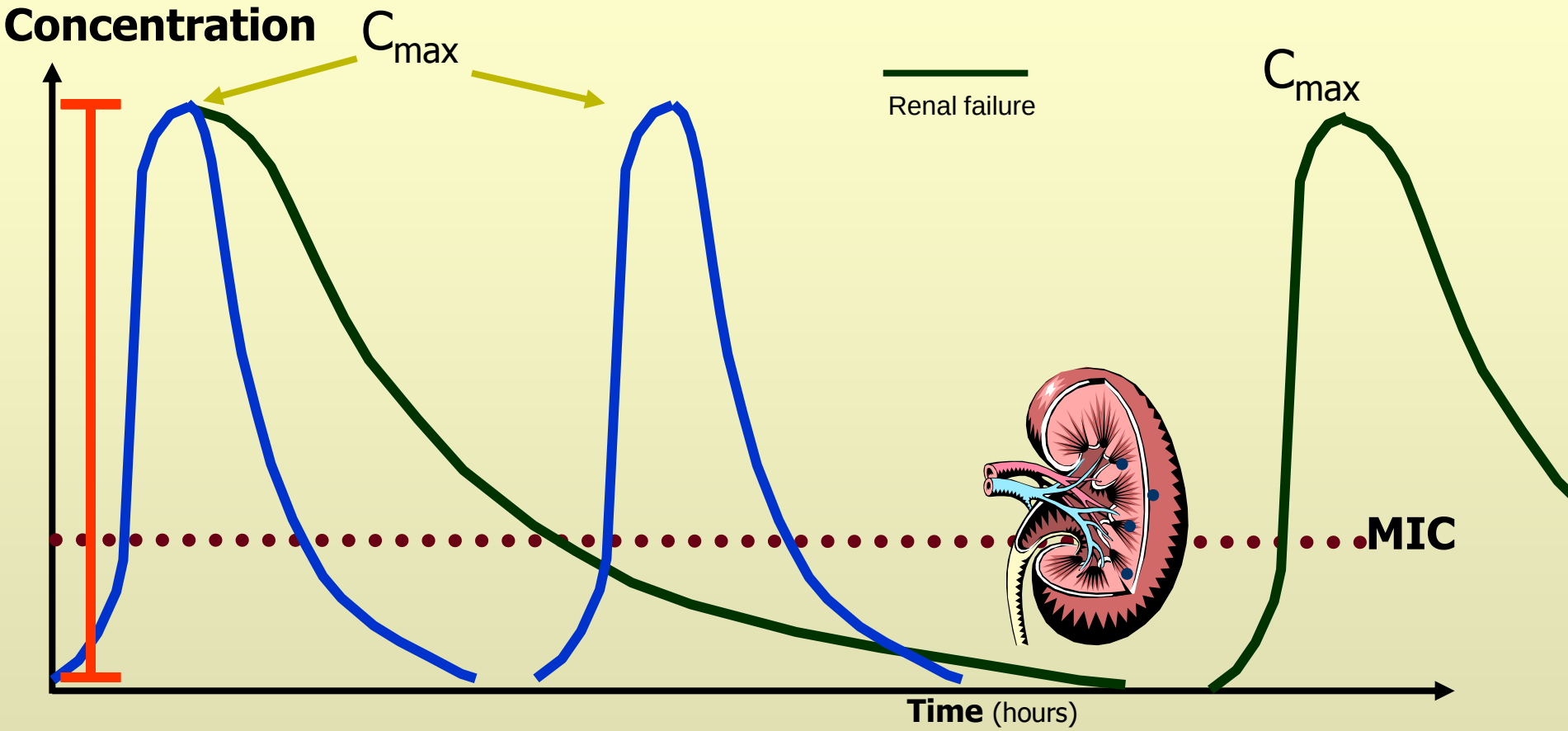
Vd of β-Lactams in critically ill patients and healthy volunteers.



Gonçalves-Pereira. Crit Care 2011, 15: R206

Patterns of Antimicrobial Activity

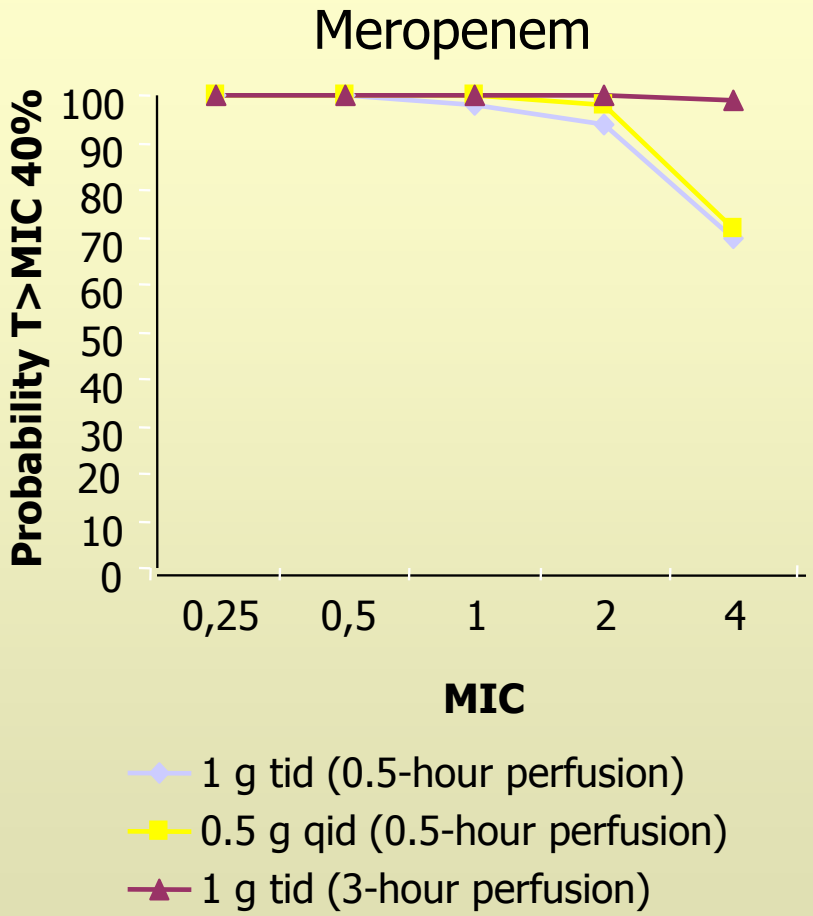
Aminoglycosides

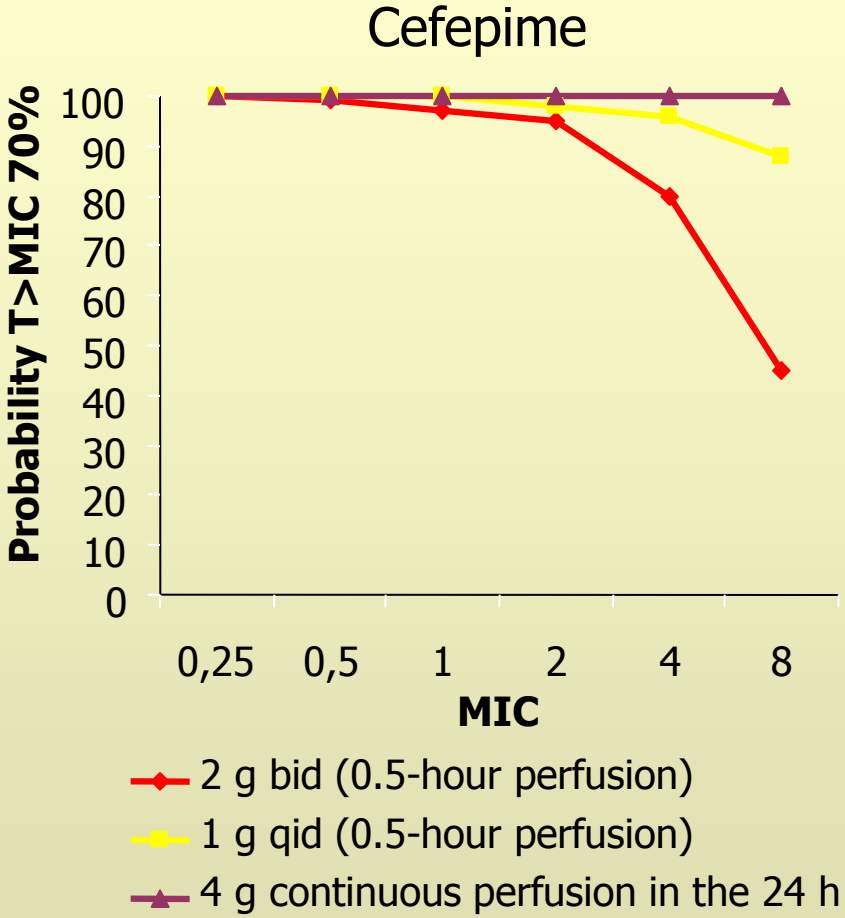


- **Pharmacodynamic parameter of efficacy: Peak/MIC**
- **Toxicity** (Renal accumulation): **Trough concentration**

Patterns of Antimicrobial Activity

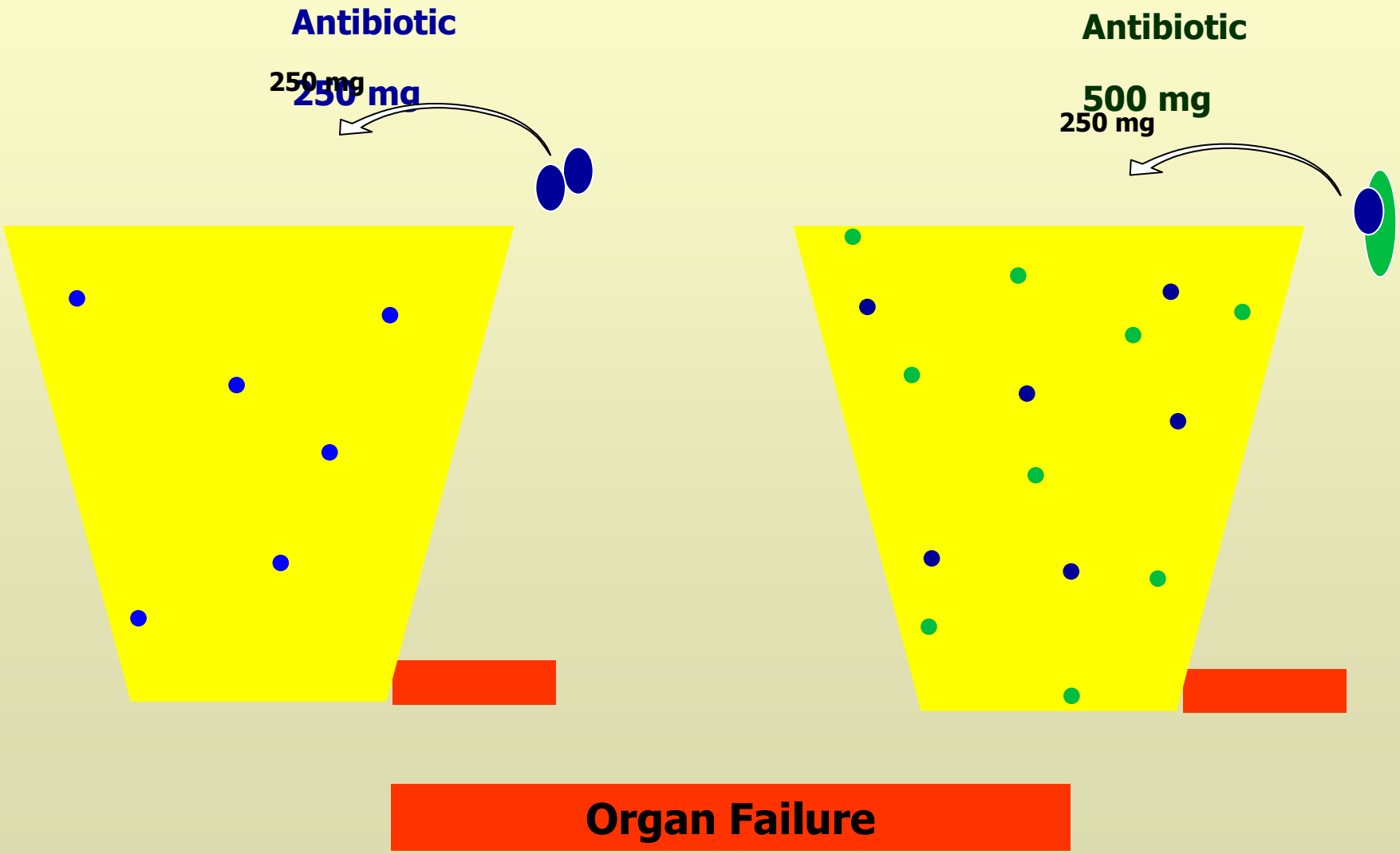
Beta-lactams





Lomaestro - Antimicrob Agents Chemother 2005
Mohr - 41st IDSA 2003

First Dose of Antibiotics



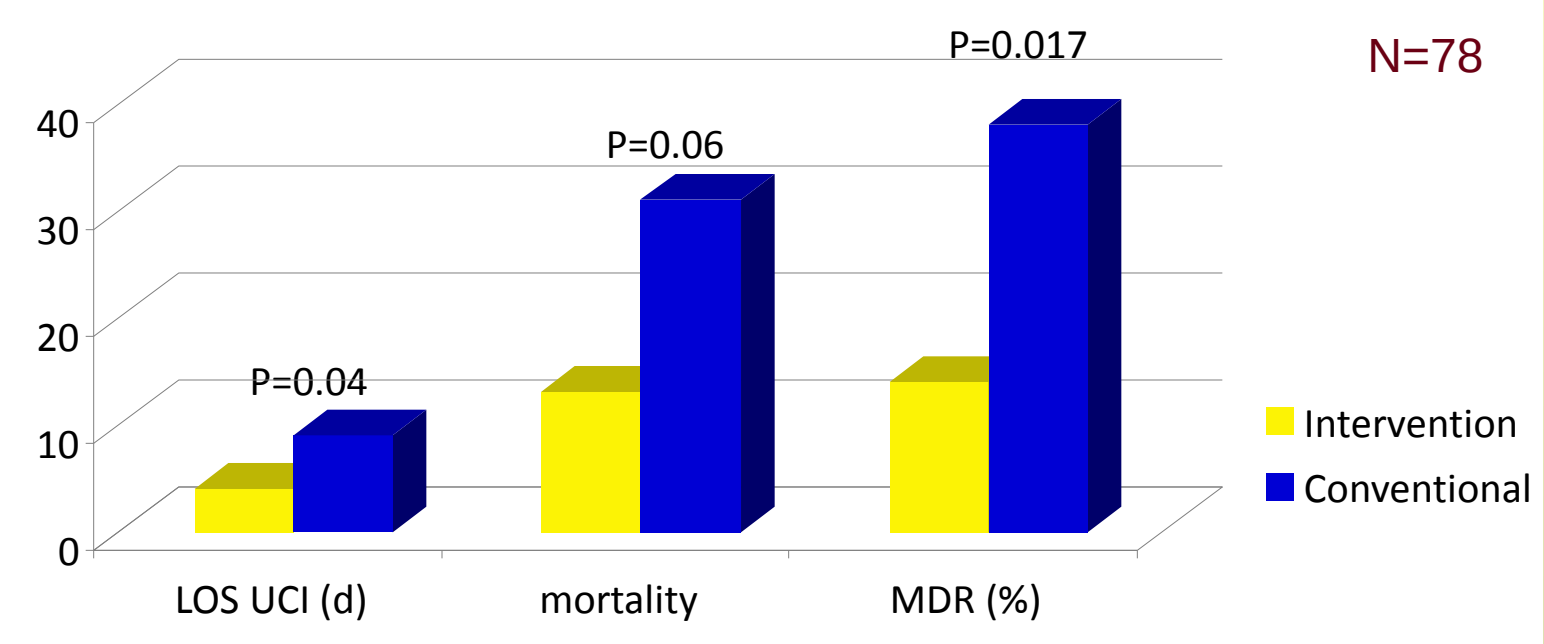
Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit

A Proposed Solution for Indiscriminate Antibiotic Prescription

NINA SINGH, PAUL ROGERS, CHARLES W. ATWOOD, MARILYN M. WAGENER, and VICTOR L. YU

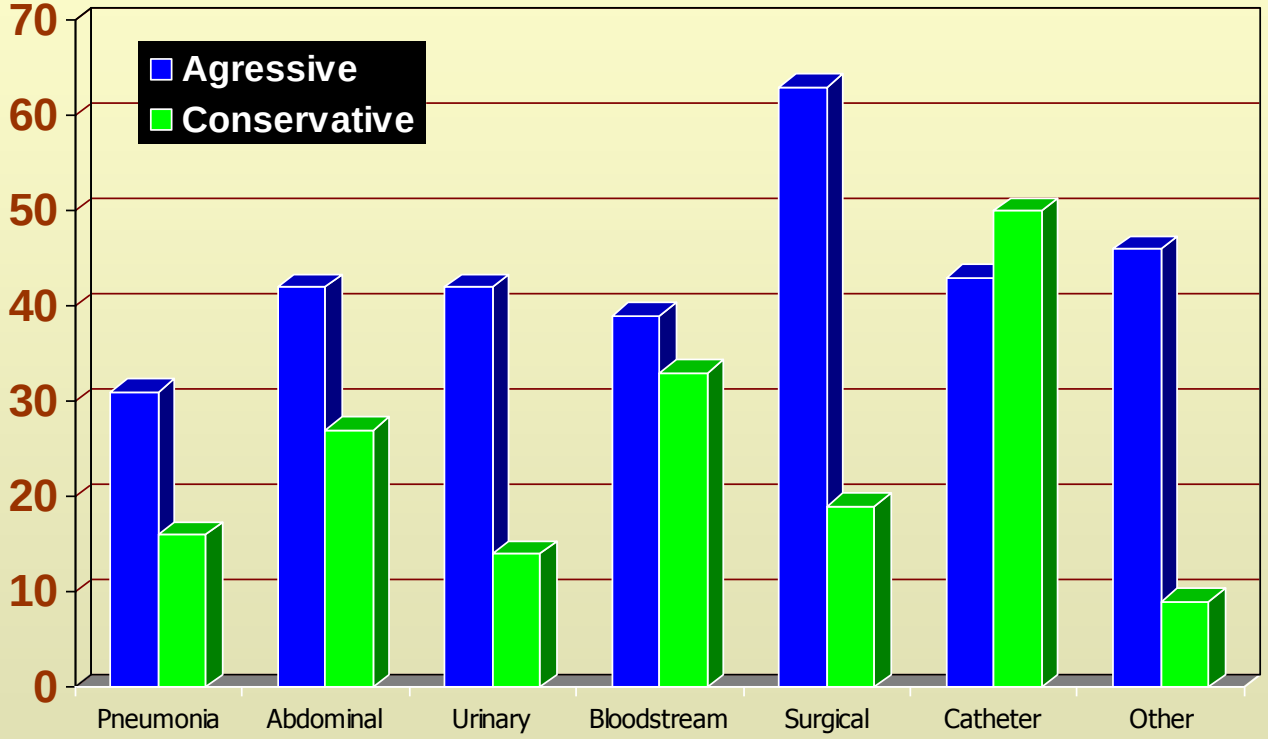
Low suspition of VAP (CPIS≤6)

Antibiotics (median) intervention 3d vs. standard 9.8d



Singh AJRCCM 2000;162:505

Time of antibiotics and Mortality



Patients with shock could have antibiotics started immediately after cultures

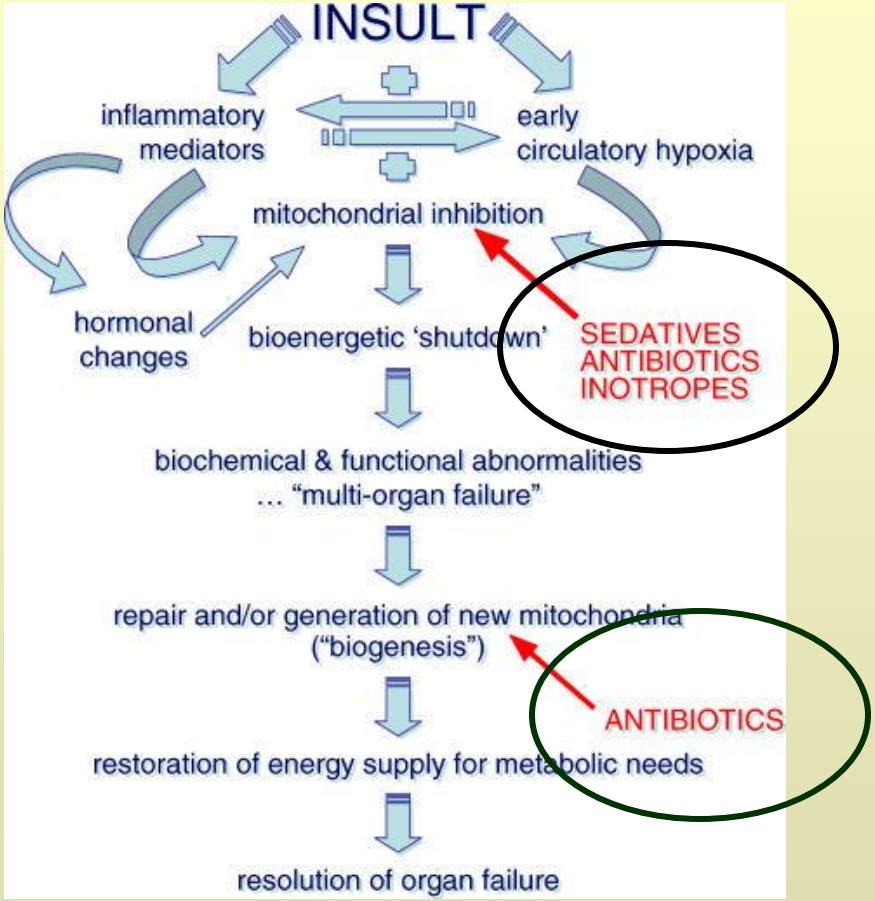
Mortality 13% vs. 27%; p=0.015; AOR 2.5 (1.5-4.0)

LOS 12.5 vs 17.7 (p=0.008)

Hranjec, Lancet Inf Dis 2012; 12:774

Can Antibiotics harm patients?

- ☞ May promote mitochondrial damage and shutdown.
- ☞ May interfere with mitochondrial biogenesis and delay recovery.

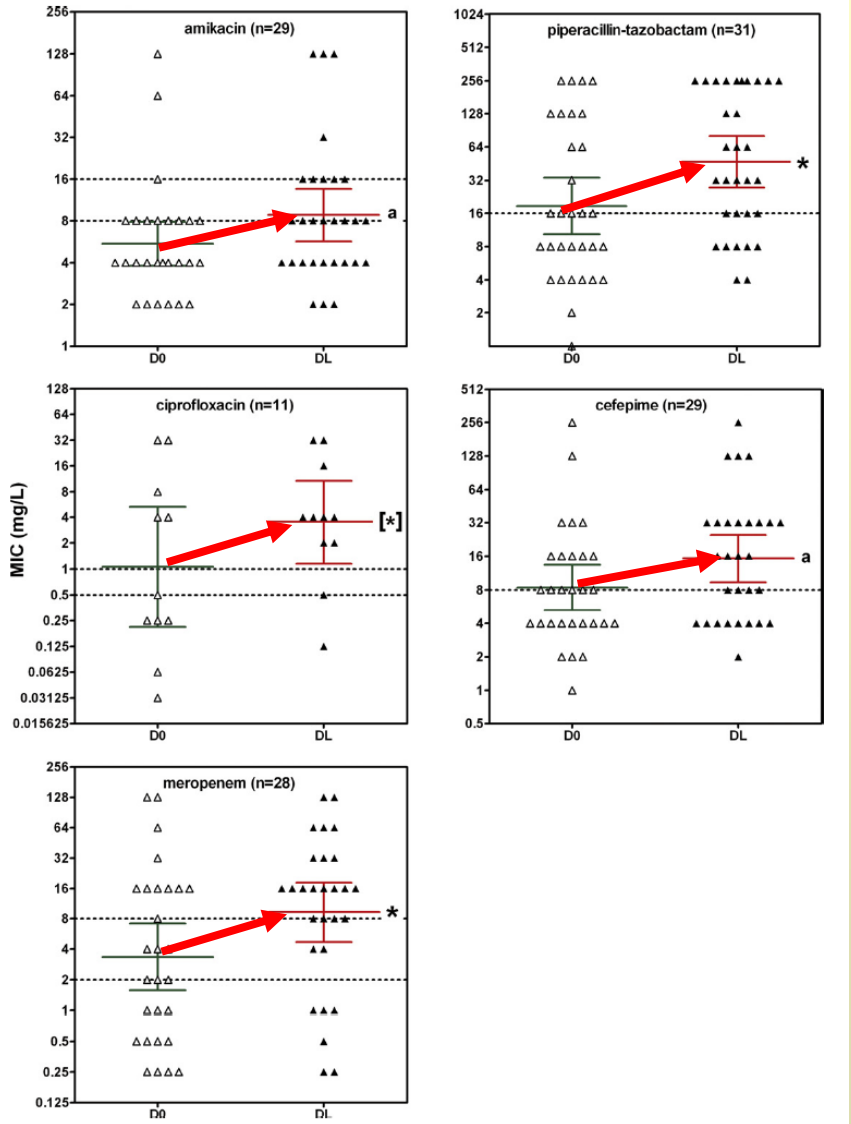


This mitochondrial toxicity may depend on the class of the antibiotic

Riesbeck. Antimicrob Agents Chemother 1990, 167

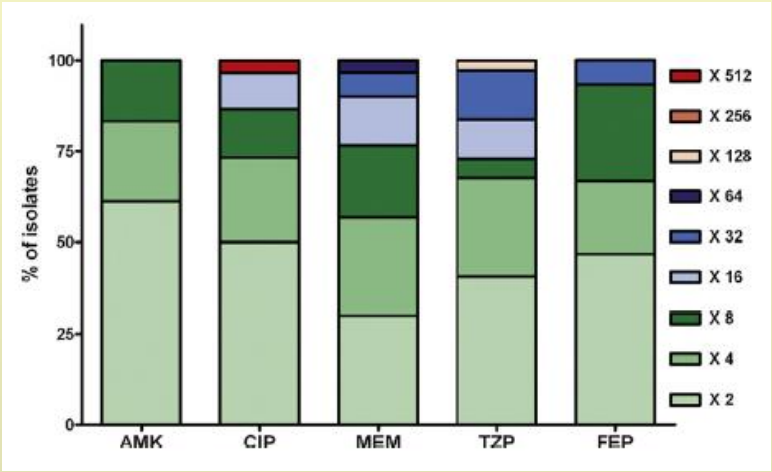
Singer. Plos Med 2005. e167

Induction of Resistance



Bacteria previously exposed to an antibiotic

Increase in the MIC



Riou Int J Antimicrob Agents 2010; 36:513

Accumulation and Toxicity

Betalactamin-induced central nervous side effects include confusion, disturbances of behaviour, hallucinations, asterixis, myoclonic jerks, and generalised convulsive or nonconvulsive seizures. Those are probably underreported but may contribute to morbidity and mortality.

Chatellier Int Care Med 2002; 28. 214

Ceftriaxone 2 g/d

Accumulation in renal failure

Cr Cl	>50 mL/min	<50 mL/min
Day 1	19,5 µg/mL	46,5 µg/mL
Day7	38,5 µg/mL	125 µg/mL

Heinemeyer Int Care Med 1990; 16; 448

Ventilator Associated Pneumonia

Dose of antibiotics

- Normalization of the increase in Vd and Cl (with sepsis resolution)

- High antibiotic concentration

Progressive normalization of PK

	2nd day	7th day	*p*
Peak concentration (µg/ml)	4.9 ±1.2	6.8 ±0.9	<0.001
Trough concentration (µg/ml)	1.17±0.65	1.10±0.3	ns
Vd (l/kg)	0.43±0.12	0.29±0.17	<0.001
T (1/2 h)	4.3 ±2.0	3.2 ±0.71	<0.05
Cl (l/kg/h)	0.07±0.02	0.05±0.01	ns
TDR (mg/kg/h)	5.14±2.43	3.98±1.67	<0.001

Triginer Intensive Care Med 1990;16:303-306

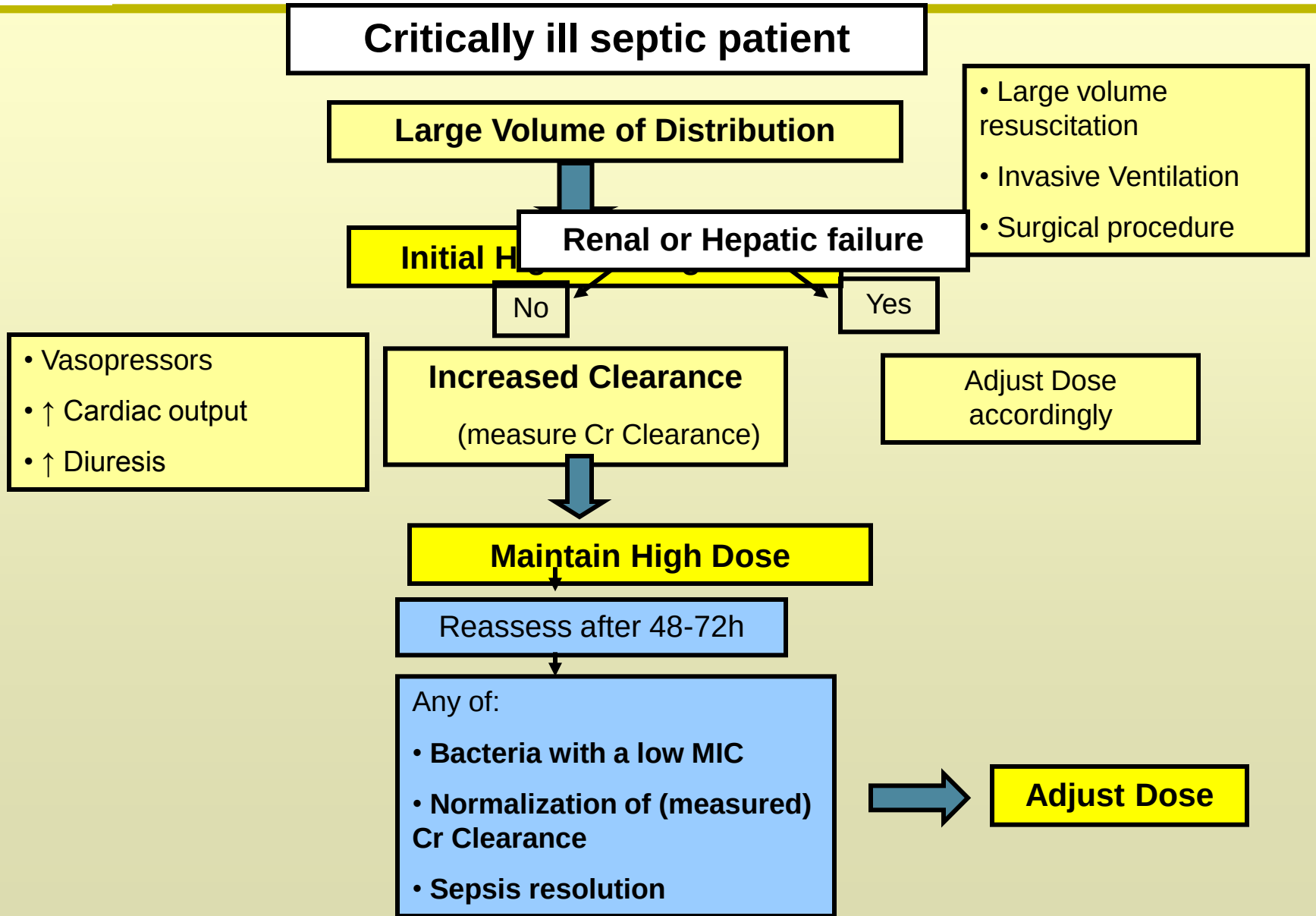
Meropenem PK

	Early	Late
SOFA	**5.5** [4.8-8.0]	**3.0** [2.8-4.5]
Vdss/Weight (L/Kg)	**0.26** [0.22-0.33]	**0.20** [0.15-0.30]
Vdss (p)/Vdss (%)	**71%** [56%-82%]	**58%** [43%-70%]
Cl (L/h)	**6.8** [3.0-7.9]	**6.0** [3.9-11.6]
Trough (mg/L)	**3.0** [2.7-5.8]	**2.5** [1.1-6.8]

Gonçalves-Pereira 2012, submitted

Dose modulation: A new concept of antibiotic therapy

JG Pereira, JA Paiva. J Crit Care, 2013; 28: 341-346



Discontinuation of Antibiotics

Discontinuation policy:

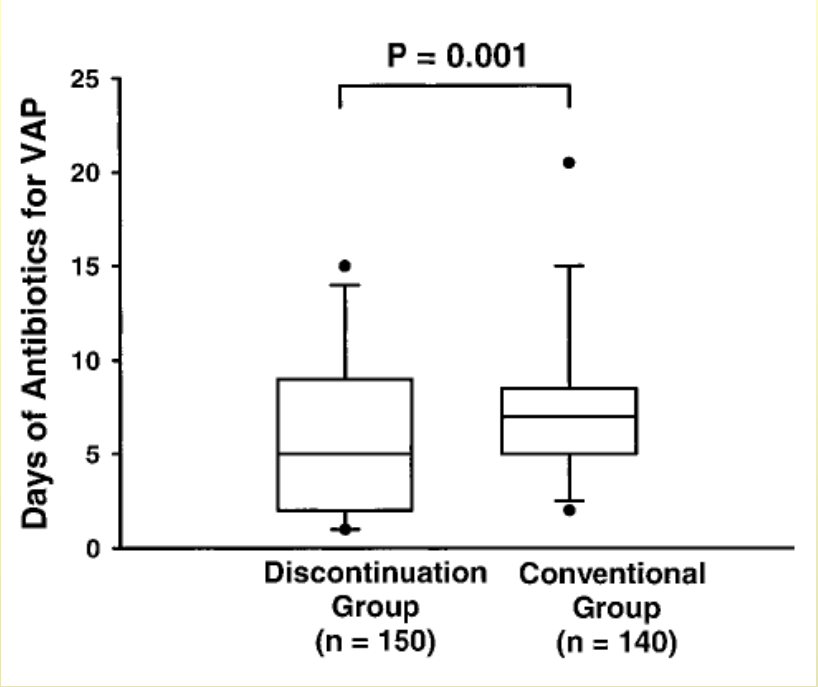
- ✓ Initial administration of adequate antibiotic treatment

  or

- ✓ Noninfectious etiology for the infiltrates

  and

- ✓ Signs and symptoms suggesting active infection had resolves



Hospital Mortality	32%	vs. 37.1%	(p=0.357)
Lenght of stay (H)	15.7	vs. 15.4	(p=0.865)
Subsequent infection	37.3%	vs. 46%	(p=0.425)

Micek Chest 2004;125:1791

Conclusões

- **O início precoce da antibioterapia deve ser restrito a situações de risco, em particular choque (expectativa armada)**
- **Os conceitos de PK/PD devem ajudar a seleccionar a posologia, integrados na restante avaliação clínica**
- **Como regra a antibioterapia pode ser limitada a um período não superior a 7 dias**
- **Os riscos de sub-dosagem por um lado e de acumulação e toxicidade por outro devem ser sempre ponderados e a dose modulada**

A antibioterapia é sempre uma arma de dois gumes, podendo também causar dano no hospedeiro e interferir com a sua ecologia.

João Gonçalves Pereira, Inf Sepsis Nov 2013, *in press*

Hospital Vila Franca de Xira

SECOND OPINION

BY ROB ROGERS

Rogers R Chest 2011;139:980-980