Hospital
Vila Franca de Xira

Community Acquired Pneumonia

Maximizing the efficacy of antibiotic therapy

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INFECÇÃO
SEPSIS

Antibiotics and Pneumonia

Survival in Bacteremic Pneumococcal Bacteremia Treated with Penicillin or Serum

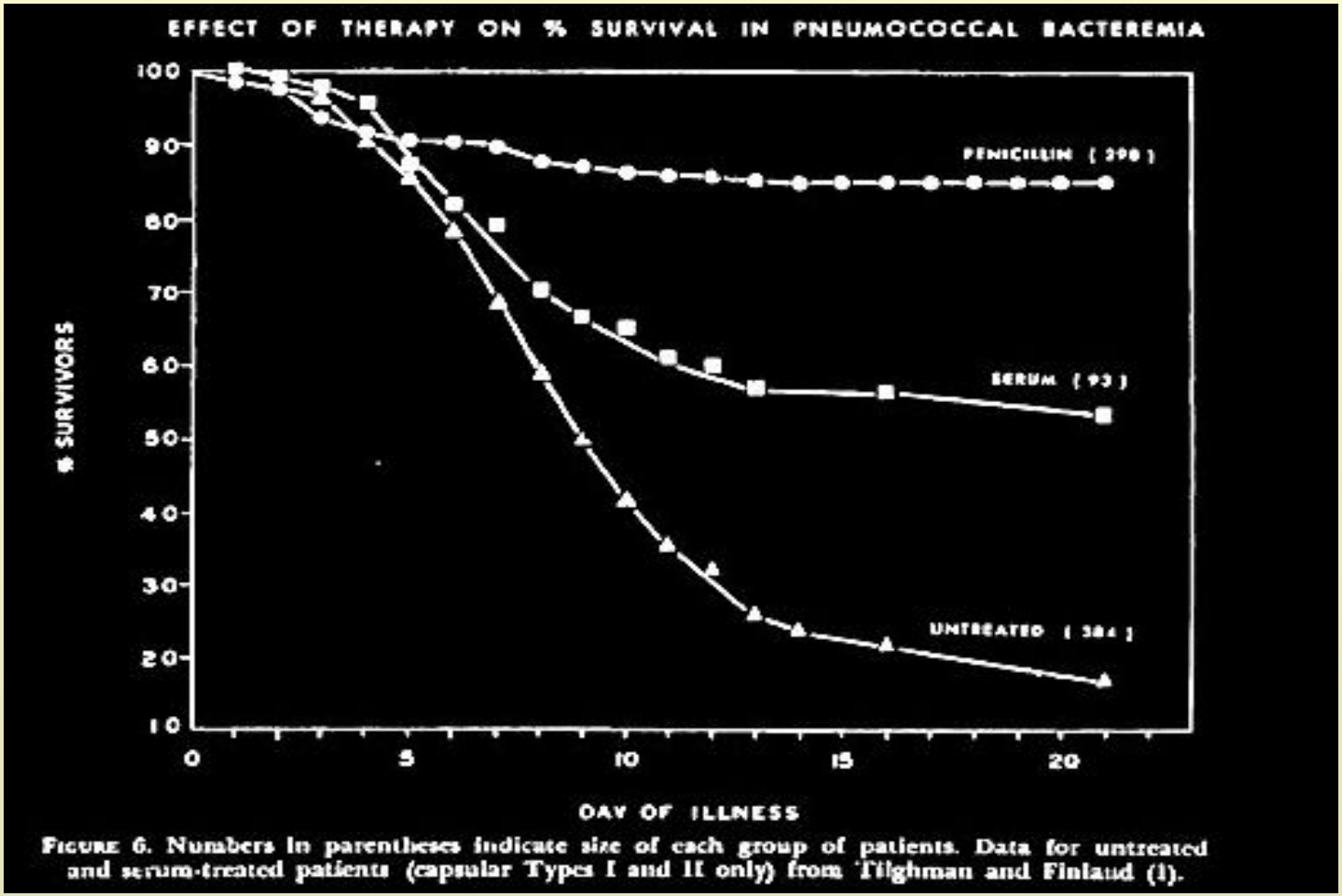


FIGURE 6. Numbers in parentheses indicate size of each group of patients. Data for untreated and serum-treated patients (capsular Types I and II only) from Tillghman and Finland (1).

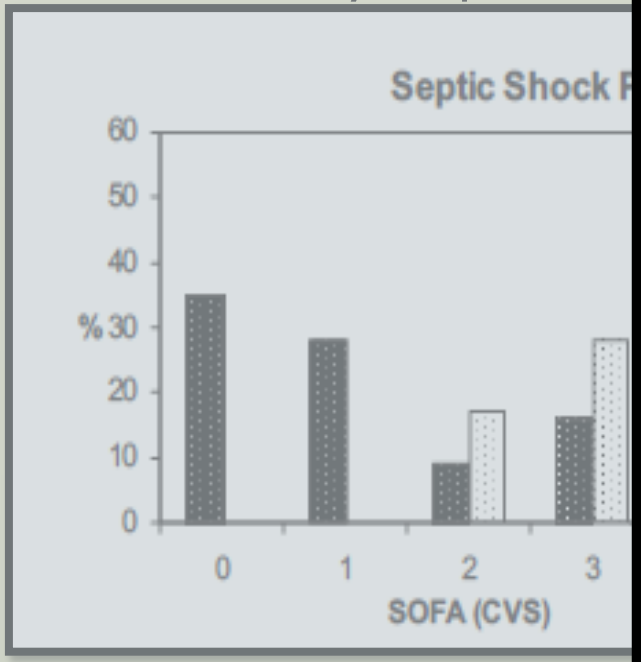
Austrian Ann Intern Med 1964;60:759

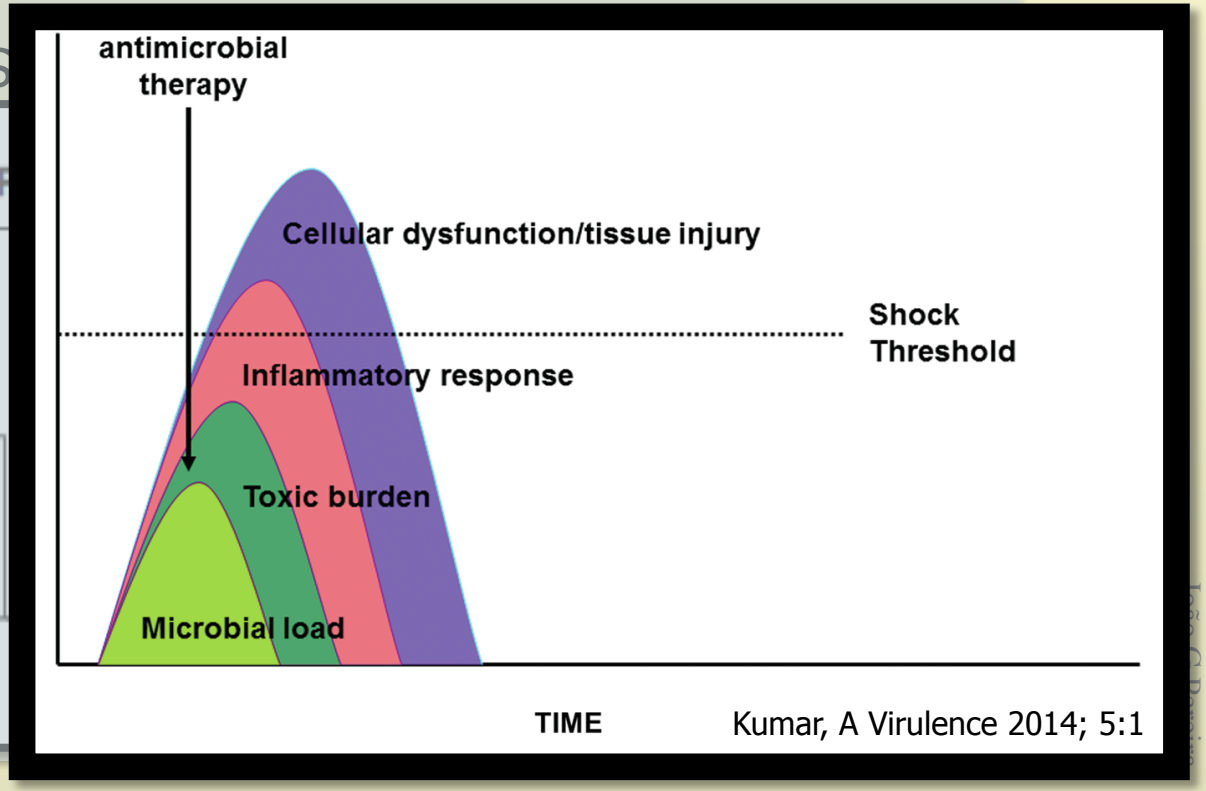
Antibiotics and Pneumonia

Time until start of antibiotic therapy (CAP)

Time to First Dose, h	Patients, No.	In-hospital Mortality, % (95% CI)	30-d Mortality, % (95% CI)	30-d Readmission, % (95% CI)	LOS Above the Median (5 d), % (95% CI)
0-2	3578	7.4 (6.6-8.3)	12.5 (11.5-13.7)	12.6 (11.5-13.8)	43.6 (41.9-45.2)
>2-4	4810	6.3 (5.6-7.0)	10.9 (10.0-11.8)	13.5 (12.5-14.5)	41.0 (39.6-42.4)
>4-6	2331	6.9 (6.0-8.1)	11.7 (10.4-13.0)	13.3 (11.9-14.8)	42.9 (40.9-45.0)
>6-8	1095	7.2 (5.8-8.9)	13.0 (11.0-15.1)	13.1 (11.1-15.3)	46.1 (43.1-49.1)
>8	1957	8.0 (6.9-9.3)	13.8 (12.3-15.5)	15.0 (13.4-16.8)	47.2 (45.0-49.5)

Community acquired S

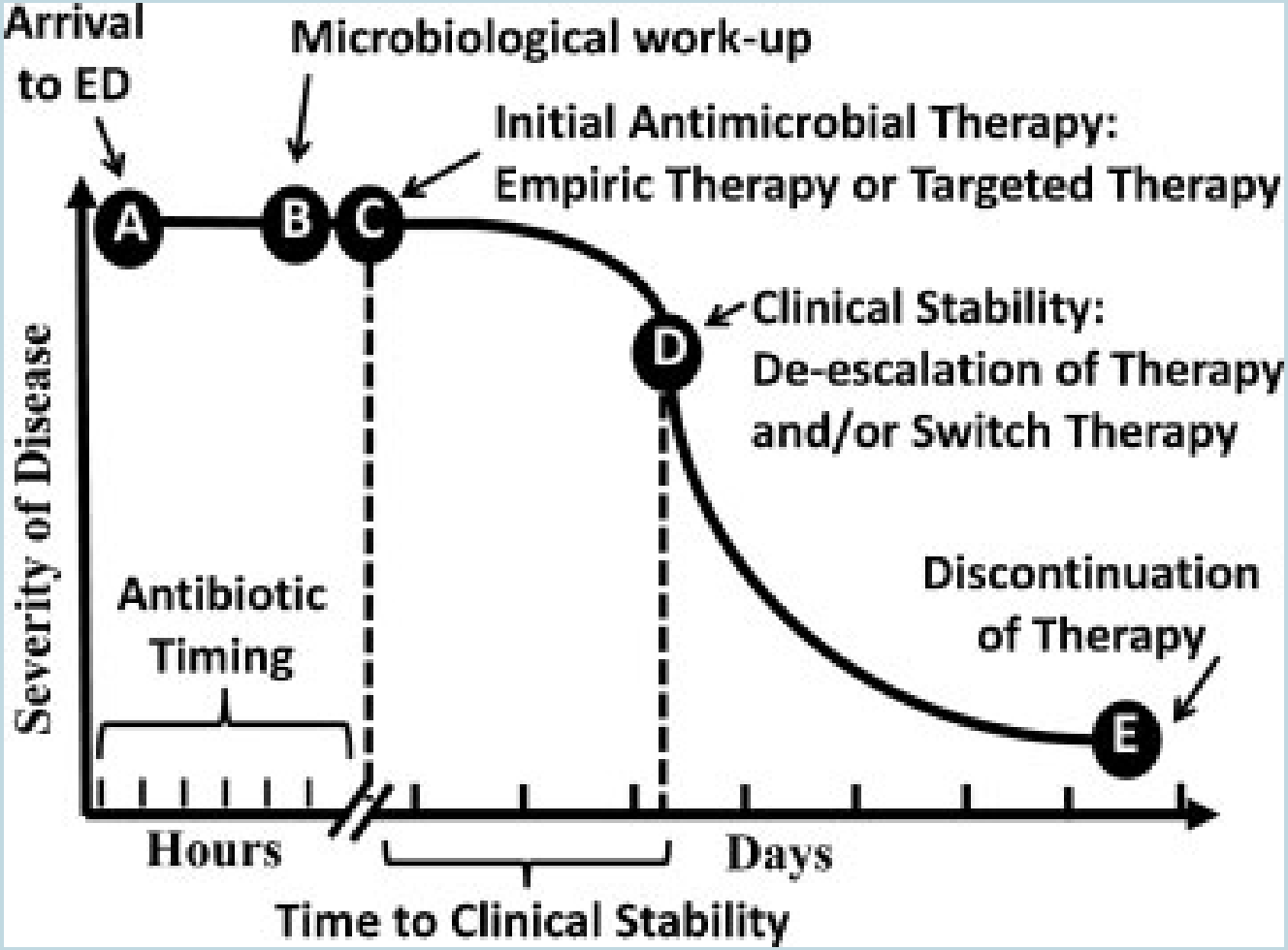




Kumar, A Virulence 2014; 5:1

Antibiotics and Pneumonia

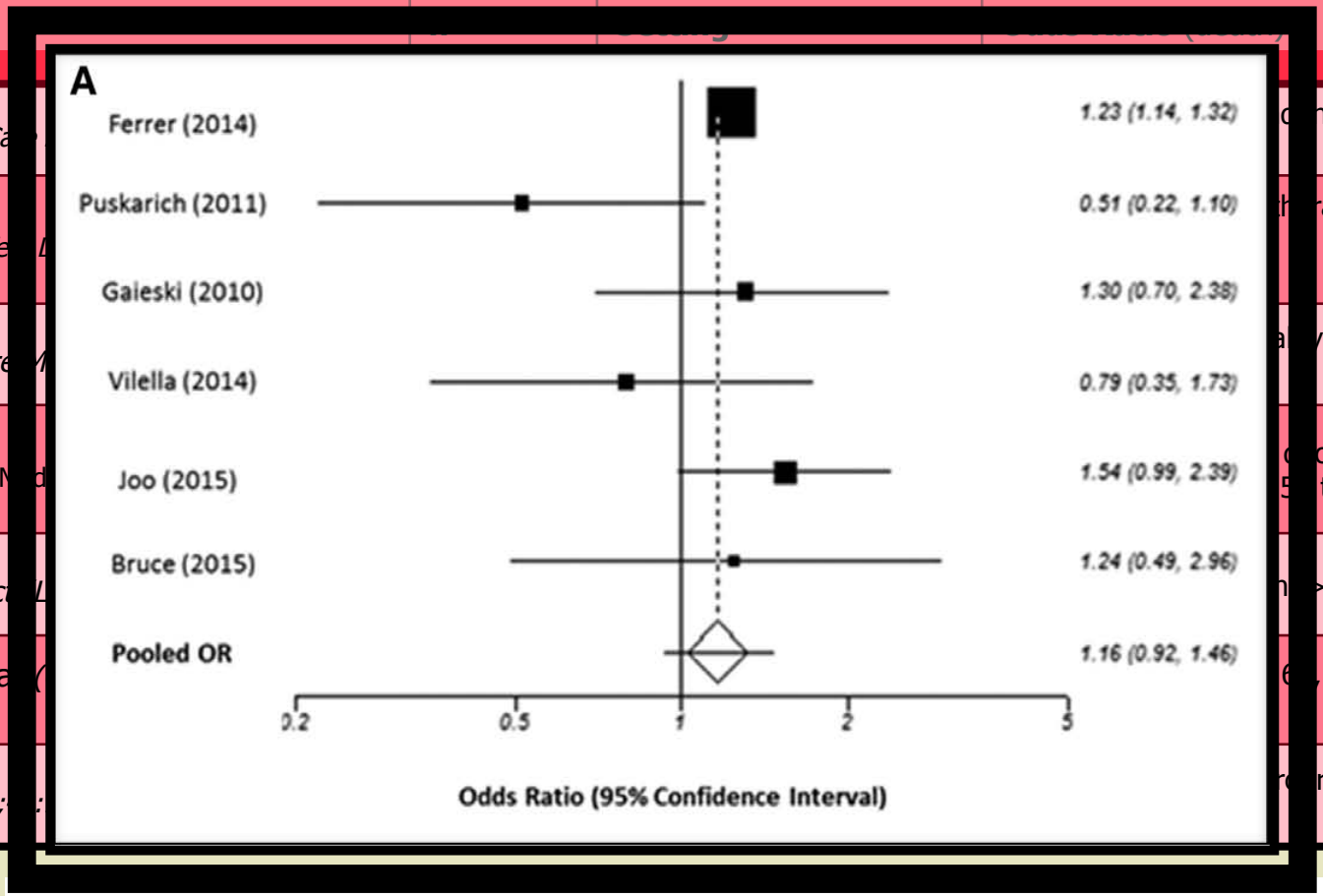
Pneumonia Bundle



Wiemken Semin Respir Crit Care Med 2012;33:213

Early antibiotics and outcome

Author	n	Setting	Odds Ratio (death)
Gai			
De Groot (*Critical Ca*			
Dar			
Hranjec *(Lancet Infe*			
Kur			
Puskarich *(Crit Care*			
App			
Villela *(Am J Emerg M*			
Lev			
Pelletier *(Surg Infect*			
Bar			
Castellanos-Ortega *(* 2010;38:1036*)*			
Fer			
Davies *(Shock 2014;*			
Jali			

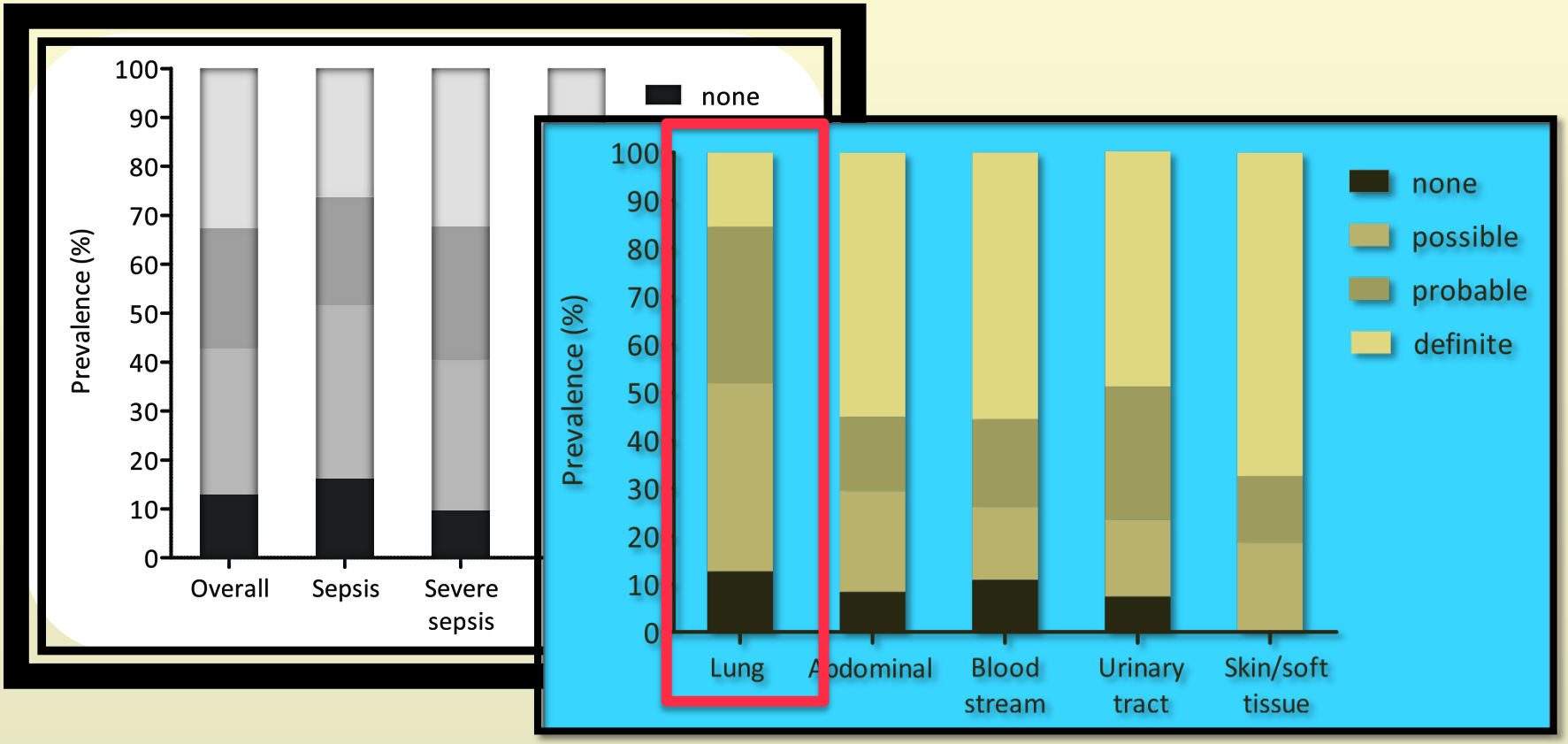


No difference in a metanalysis (11 studies included). OR 1.16

Sterling Crit Care Med. 2015;43:1907

Accuracy of sepsis diagnosis

Infection rate in patients with presumed "sepsis" upon presentation

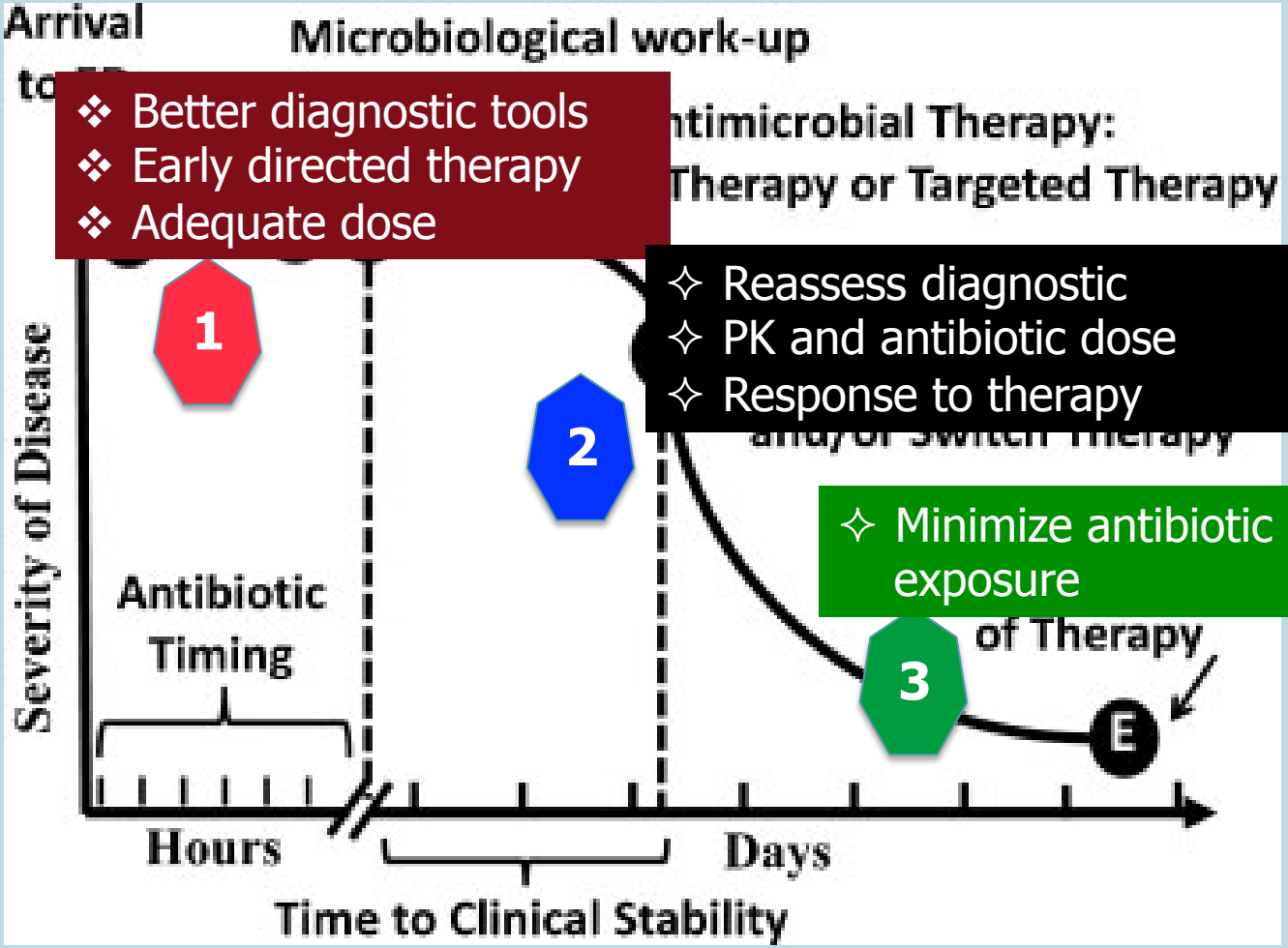


Klein Klouwenberg Crit Care 2015;19:319

- Over 50% of patients with suspected pneumonia probably did not had infection
- **Antibiotics are of no use if patients are not infected** (harm?)

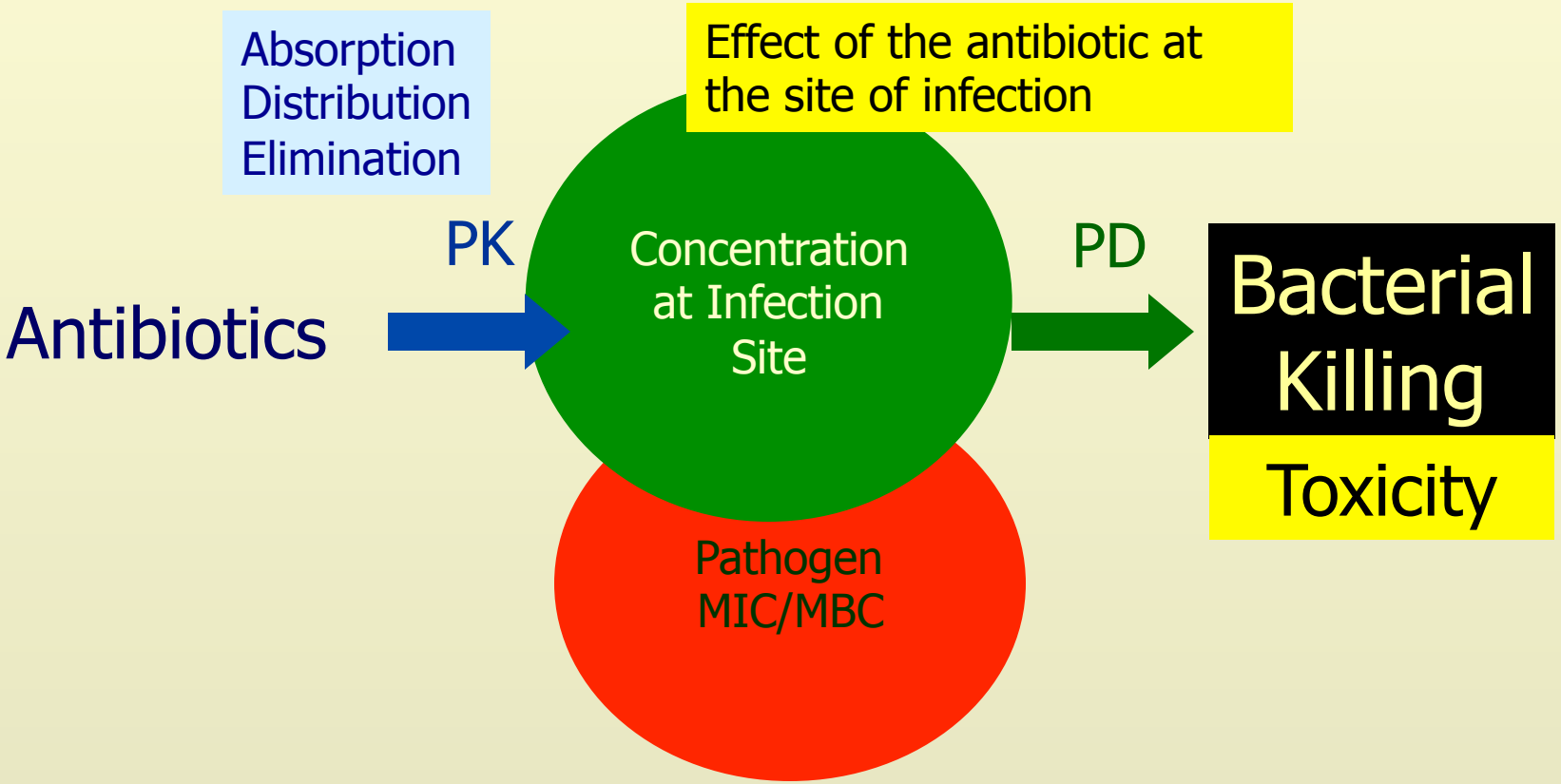
Antibiotics and Pneumonia

Pneumonia Bundle



Wiemken Semin Respir Crit Care Med 2012;33:213

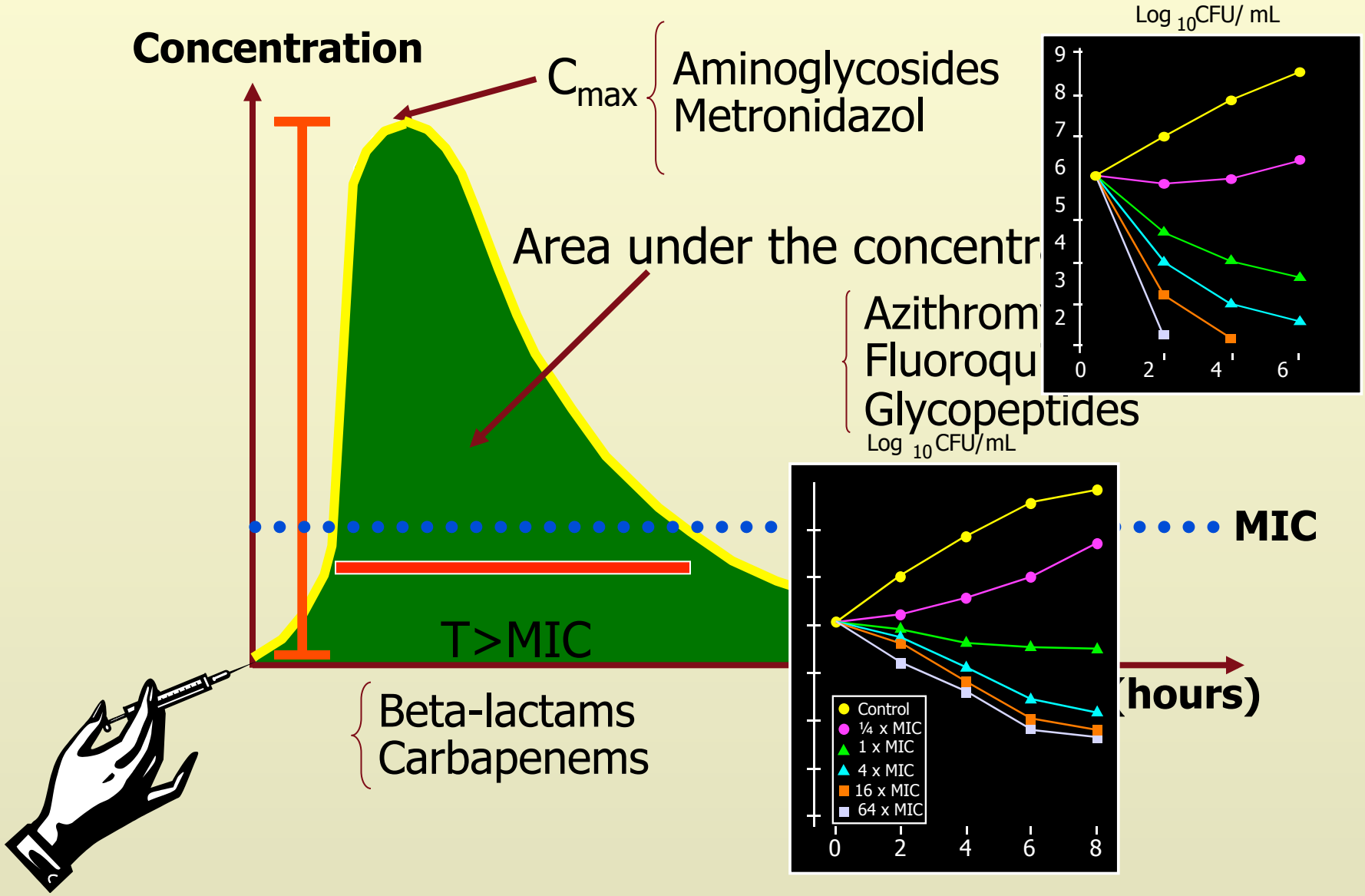
Antimicrobial dose
Pharmacokinetics



Dose antibiotics to maximize its exposure to bacteria

Craig WA - CID 1998; 26.1

Patterns of Antimicrobial Activity



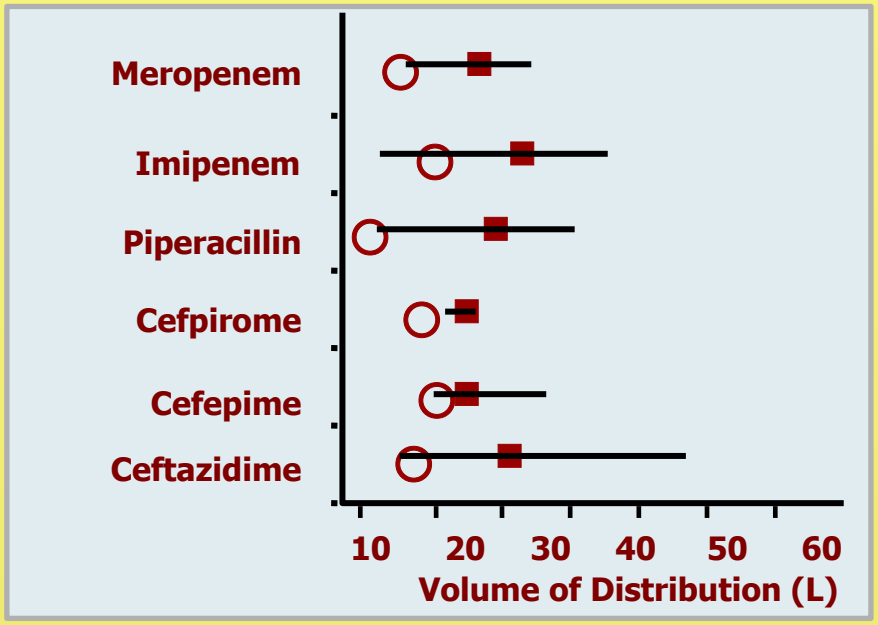
Gonçalves-Pereira and Póvoa *Critical Care* 2011, **15**:R206
http://ccforum.com/content/15/5/R206

CRITICAL CARE

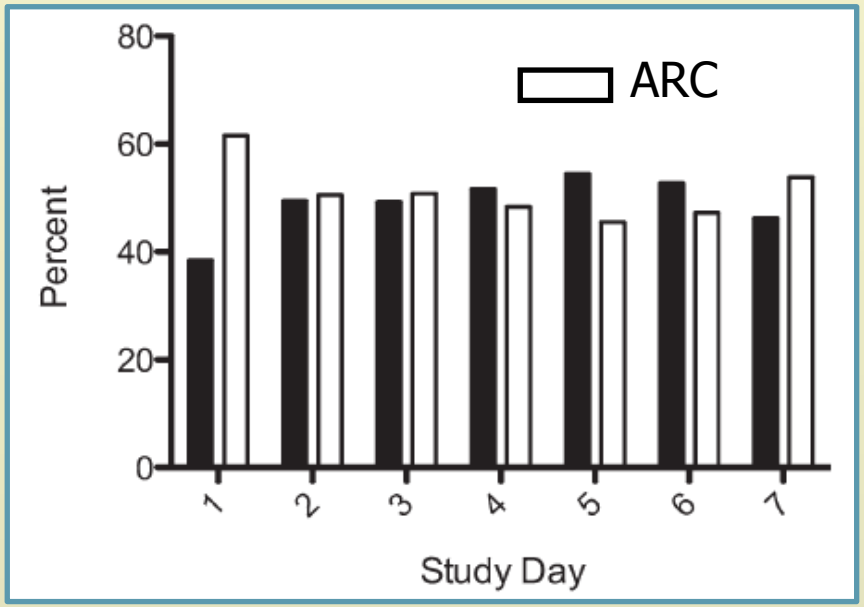
Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams

- ✓ Two fold variability of PK parameters (Vd and Cl)
- ✓ Usually increase
- ✓ No clear correlation with clinical parameters

Augmented Volume of Distribution



Augmented renal Clearance



Udy, Baptista Crit Care Med 2014; 42:520

Dose of Antibiotics

Obesity

Variable	Adjusted	
	OR (95% CI)	P-Value
1. Sex (Reference: Male)	0.88 (0.76–1.03)	0.106
2. Age		
20–34 yrs	1.00 (0.78–1.27)	0.974
35–49 yrs	1.03 (0.84–1.26)	0.812
50–64 yrs	0.99 (0.82–1.20)	0.954
65–70 yrs (Reference)	–	–
3. Socioeconomic Status		
Low Income	1.00 (0.85–	
Middle Income (Reference)	–	
High Income	0.78 (0.56–	
4. BMI Category		
Normal (Reference)	–	
Overweight	1.06 (0.89–	
Obese	1.26 (1.03–	
5. Alcohol Consumption		
Non-drinker	1.20 (1.01–	
Moderate (Reference)	–	
Heavy	0.98 (0.72–	
6. MRSA	2.33 (1.78–	
7. History of Antibiotic Use	1.27 (1.08–	

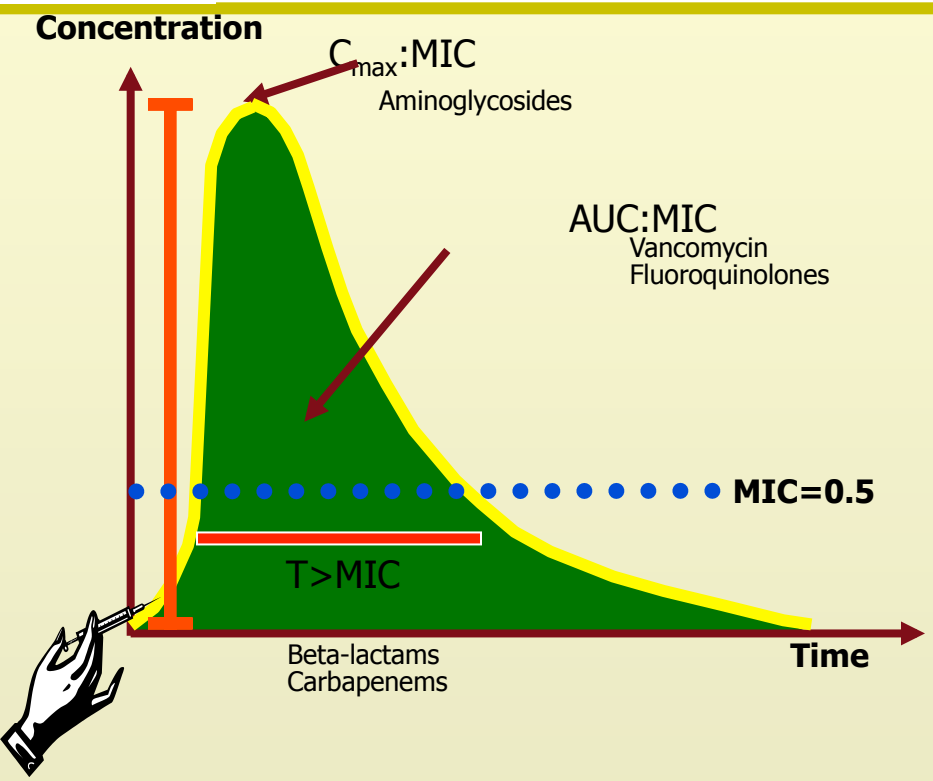
KEY POINTS

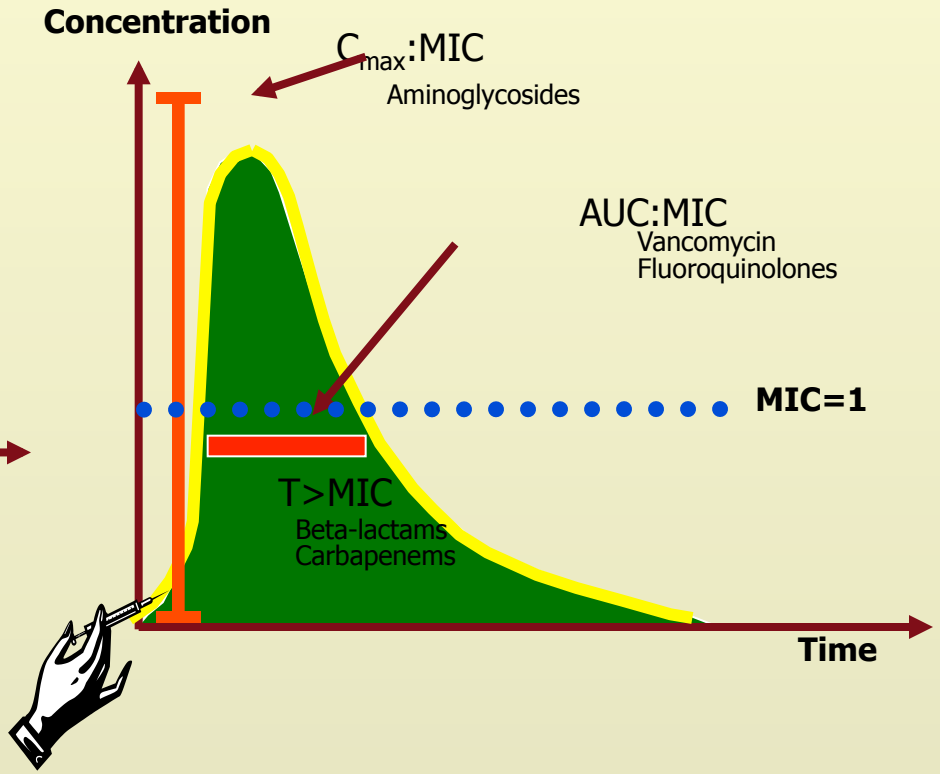
- Of the 828 (13.4%) persons who suffered an antibiotic treatment failure (ATF) event, nearly 64% were either overweight or obese.
- Significant predictors of ATF were obesity, antibiotic resistance, recent history of antibiotic use, and being a non-drinker
- Alternative antibiotic dosing strategies may be necessary when treating obese patients for acute infections as a means of reducing the risk of ATF.

Longo. Pharmacoepidemiology and Drug Safety 2013; 22: 970

Patterns of Antimicrobial Activity

MIC and resistance





- ✧ Increase in MIC 0.5 → 1mg/L: Bacteria remain sensitive.
- ✧ However AUC:MIC and Cmax:MIC decrease to one half; T>MIC also decreases
- ✧ Changes in PK may impact clinical efficacy

Bacterial load and mortality

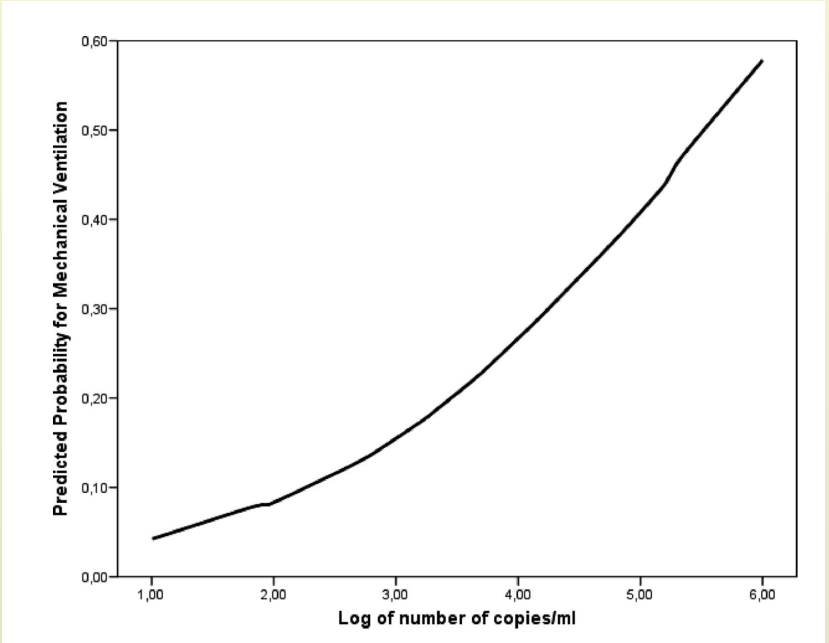
Pneumococcal Pneumonia n=353

Rt-PCR positive – 26,3% (36,5% positive BC)

Septic shock – OR 6.29

Mech. Ventilation – OR 7.96

Mortality – OR 7.08



Patients with positive Rt-PCR

Bacterial Load > 10^3cop/mL (29%)

Shock OR 8 Mech. Vent OR 10.5

Mortality OR 5.4

Rello Chest 2009;136:832

Selection of initial antibiotics

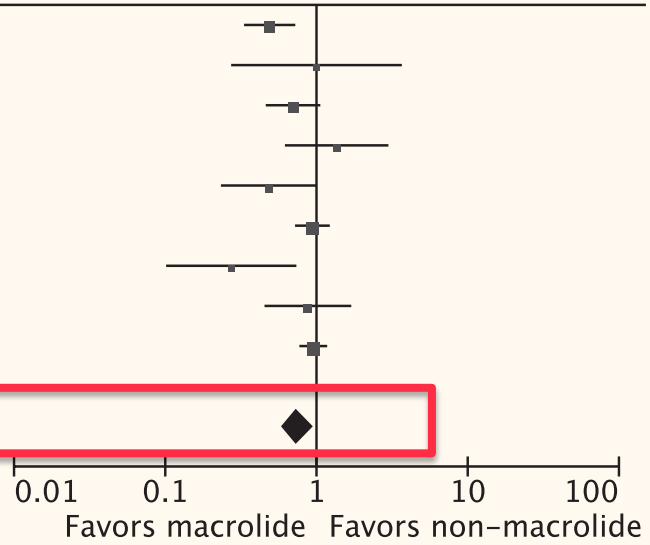
Single vs. double

Use of a macrolide in CAP

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Arnold 2013	-0.713	0.199	15.0%	0.49 [0.33, 0.72]
Bratzler 2008	0	0.663	3.1%	1.00 [0.27, 3.67]
Bratzler 2008	-0.357	0.212	14.3%	0.70 [0.46, 1.06]
Karhu 2013	0.307	0.402	6.9%	1.36 [0.62, 2.99]
Martin-Loeches 2010	-0.73	0.37	7.8%	0.48 [0.23, 1.00]
Rodrigo 2013	-0.062	0.135	18.8%	0.94 [0.72, 1.22]
Shorr 2013	-1.298	0.506	4.9%	0.27 [0.10, 0.74]
Sligl 2013	-0.131	0.337	8.8%	0.88 [0.45, 1.70]
Wilson 2012	-0.049	0.108	20.4%	0.95 [0.77, 1.18]
Total (95% CI)			**100.0%**	**0.75 [0.58, 0.96]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 18.68$, df = 8 (P = 0.02); $I^2 = 57\%$

Test for overall effect: Z = 2.31 (P = 0.02)



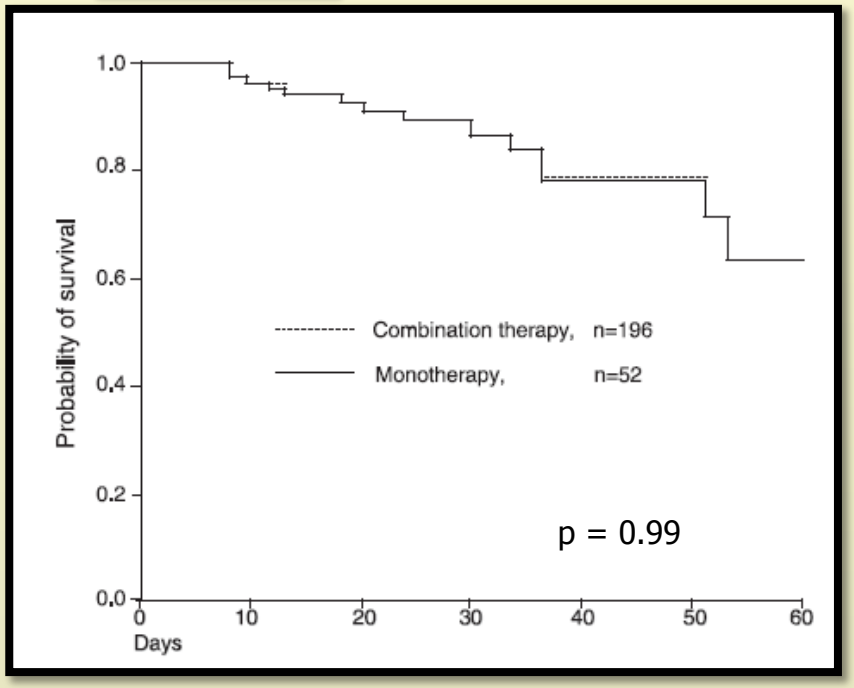
Sligl Crit Care Med 2014; 42:420

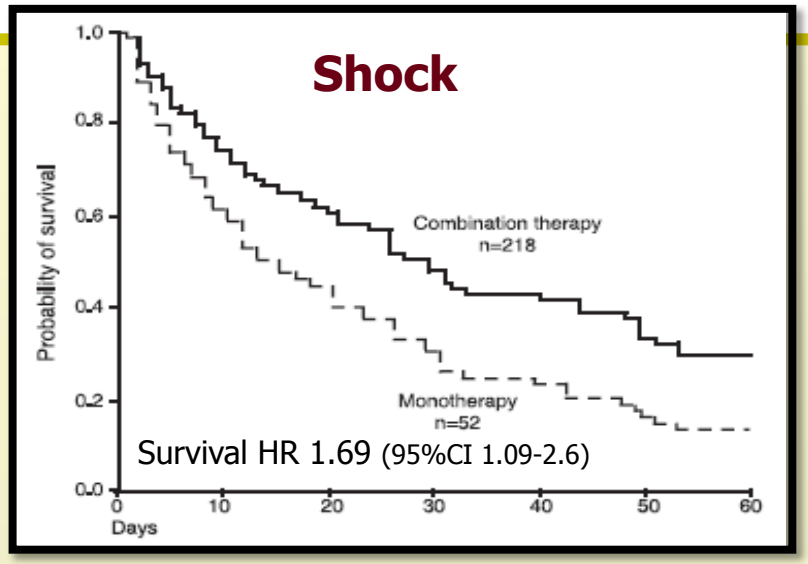
Selection of initial antibiotics

Single vs. double

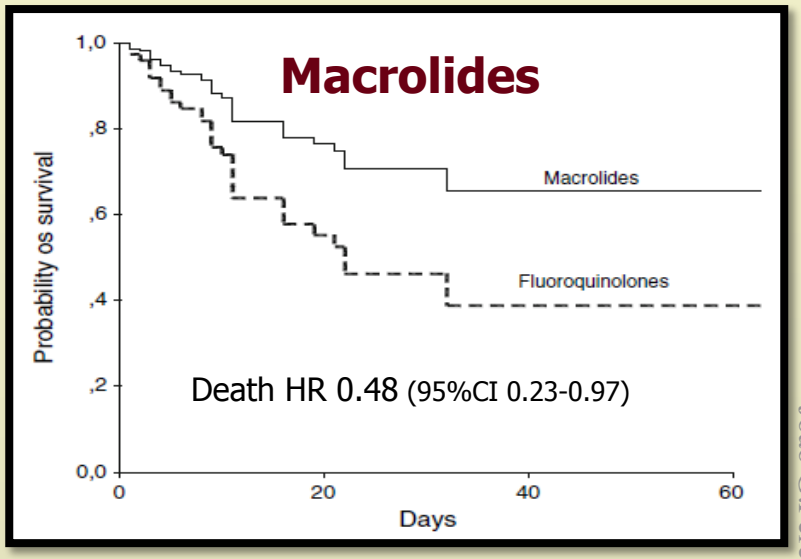
The CAPUCI study

No Shock





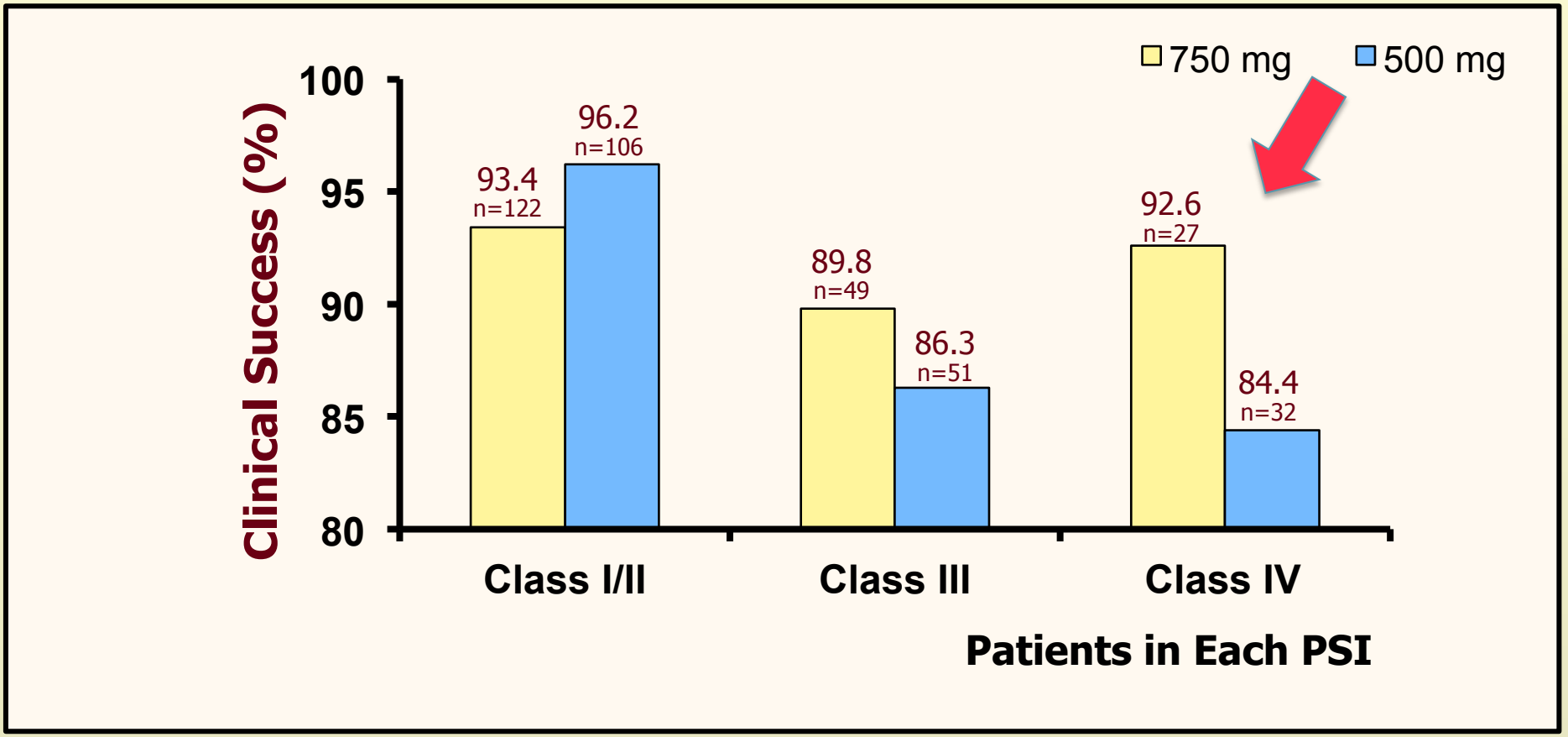
Rodriguez Crit Care Med 2007;35:1493



Martin-Loeches Intensive Care Med 2010; 36:612

Dose of Antibiotics

Clinical Success by PSI Class



*Clinically evaluable patients at the 7- to 14-day post therapy visit

Dunbar Clin Infect Dis. 2003;37:752

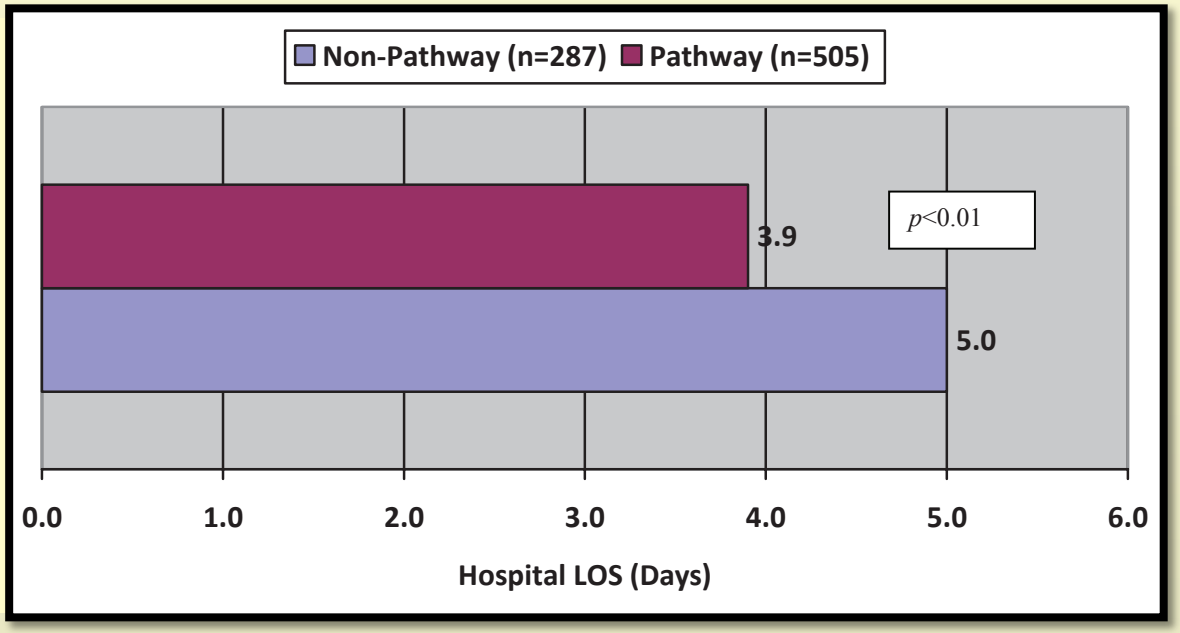
Frei *et al. BMC Infectious Diseases* 2011, **11**:188
http://www.biomedcentral.com/1471-2334/11/188

BMC Infectious Diseases

A clinical pathway for community-acquired pneumonia: an observational cohort study

PK/PD guided dose

- ✧ Lower adjusted 90d mortality (p=0.02)
- ✧ Lower LOS (3.9 vs. 5d, p<0.001)
- ✧ Lower Costs ($2485 vs. $3281, p=0.02)



Frei, BMC Infect Dis 2011,11: 188

N=432

A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

Joel M. Dulhunty[1,2], Jason A. Roberts[1,2,3], Joshua S. Davis[4,5], Steven A. R. Webb[6,7], Rinaldo Bellomo[8,9], Charles Gomersall[10,11], Charudatt Shirwadkar[12], Glenn M. Eastwood[8], John Myburgh[13,14], David L. Paterson[15,16], Therese Starr[1,2], Sanjoy K. Paul[17], and Jeffrey Lipman[1,2]; for the BLING II Investigators for the ANZICS Clinical Trials Group*

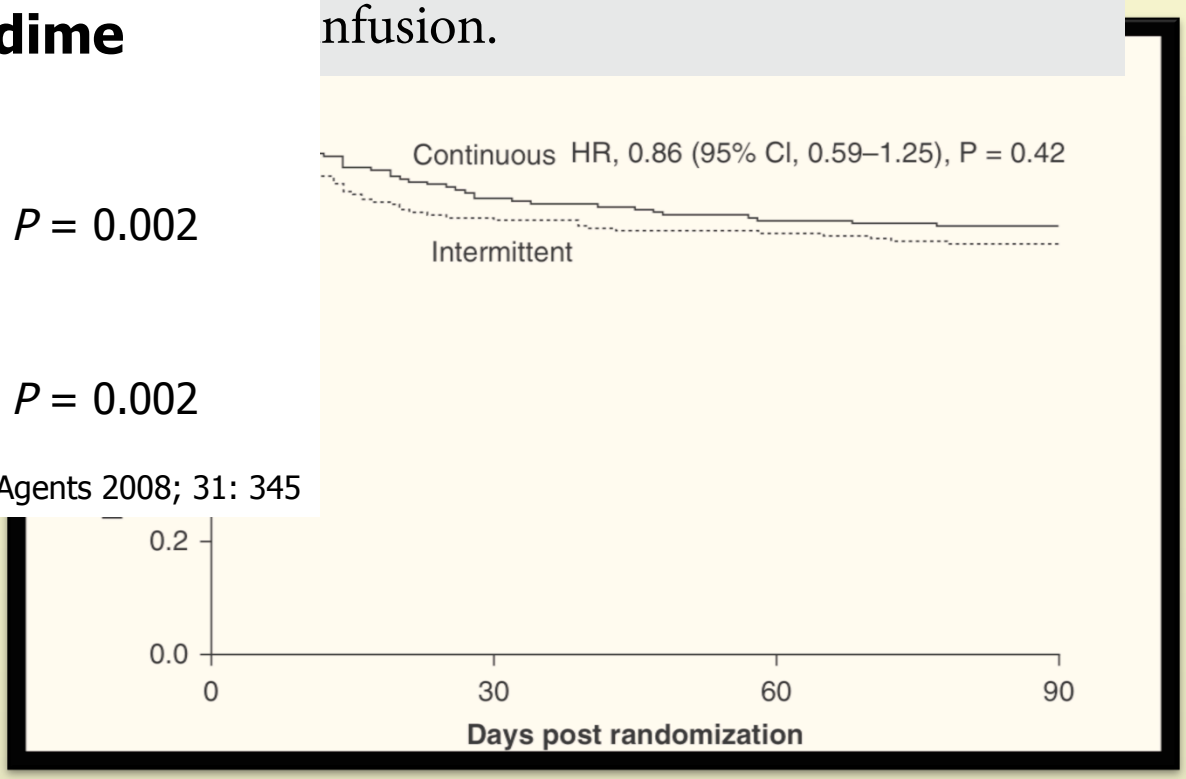
Clinical success

Cefepime or ceftazidime

- AUIC≥250
  Cure 79% vs. 33%; *P* = 0.002
- *T*>MIC of 100%
  Cure 82% vs. 33%; *P* = 0.002

Mckinnon. Int J Antimicrob Agents 2008; 31: 345

ents with severe sepsis, there was no
3-lactam antibiotic administration
nfusion.



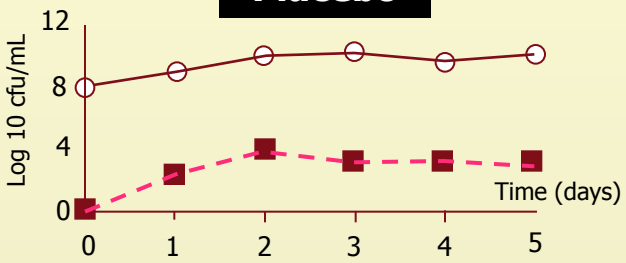
Dulhunty Am J Resp Crit Care Med 2015; 192: 1298

HR 0.91 (0.63-1.31)

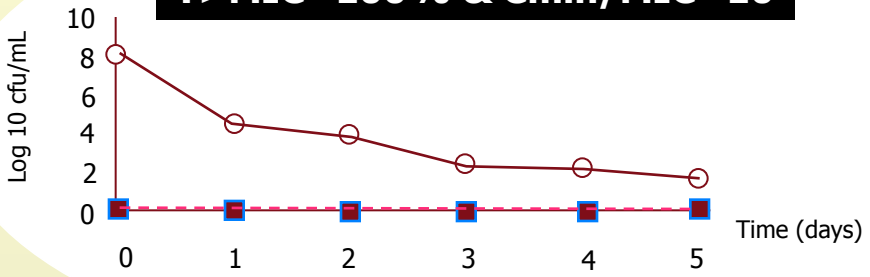
João G.Pereira

Optimization of minimum concentration/MIC ratio

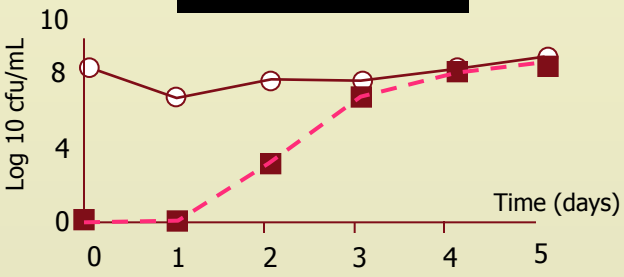
Placebo



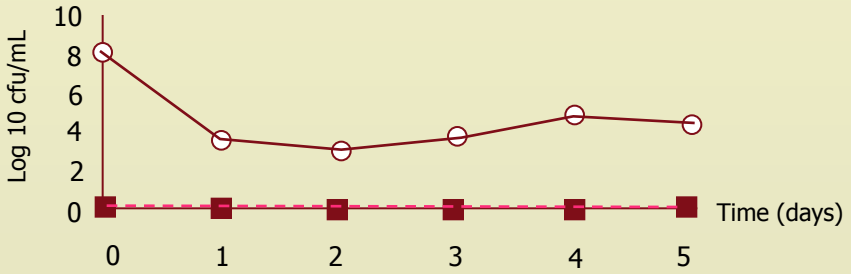
T>MIC=100% & Cmin/MIC=10



T>MIC=84%



T>MIC=100% Cmin/MIC=1.7+ tobramycin

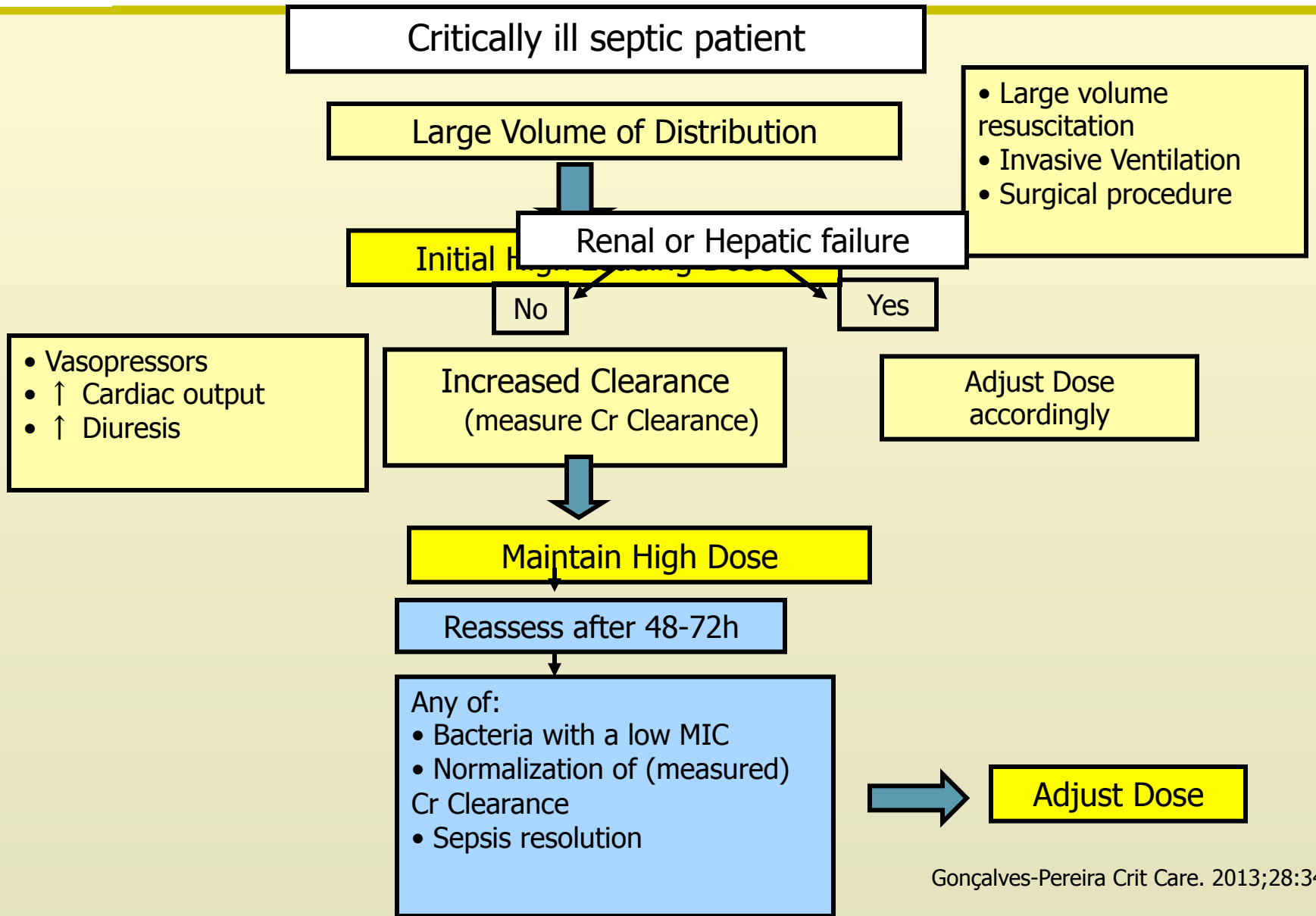


Tam Antimicrob Agents Chemother 2005; 49. 4920

Journal of Critical Care

Dose modulation: A new concept of antibiotic therapy in the critically ill patient?☆,☆☆,★

Joao Goncalves-Pereira MD[a,*], José-Artur Paiva MD, PhD[b]



Gonçalves-Pereira Crit Care. 2013;28:341

Accumulation and Toxicity

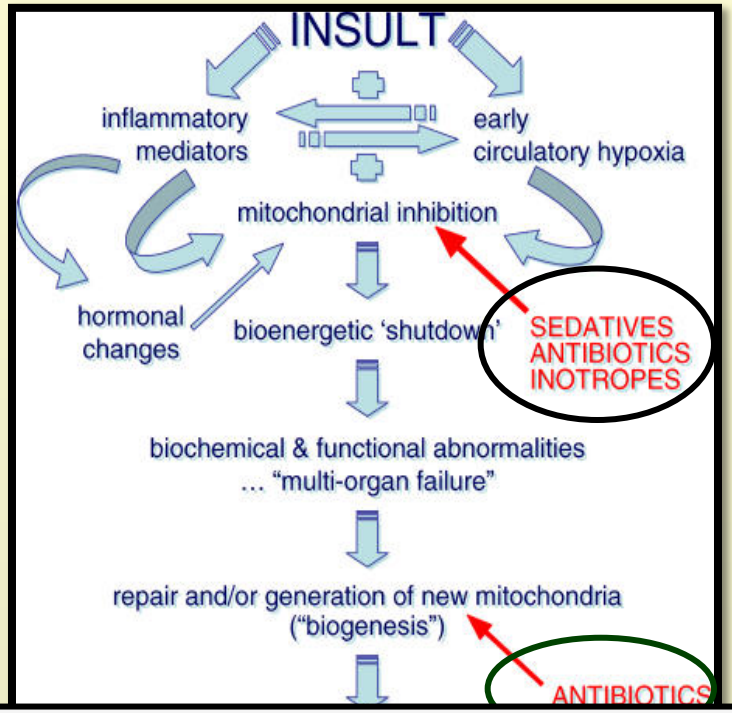
Ceftriaxone 2 g/d – Increase 2-3* from D1 to D7

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

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



☞ May promote mitochondrial damage and shutdown.

☞ May interfere with mitochondrial biogenesis and delay recovery.

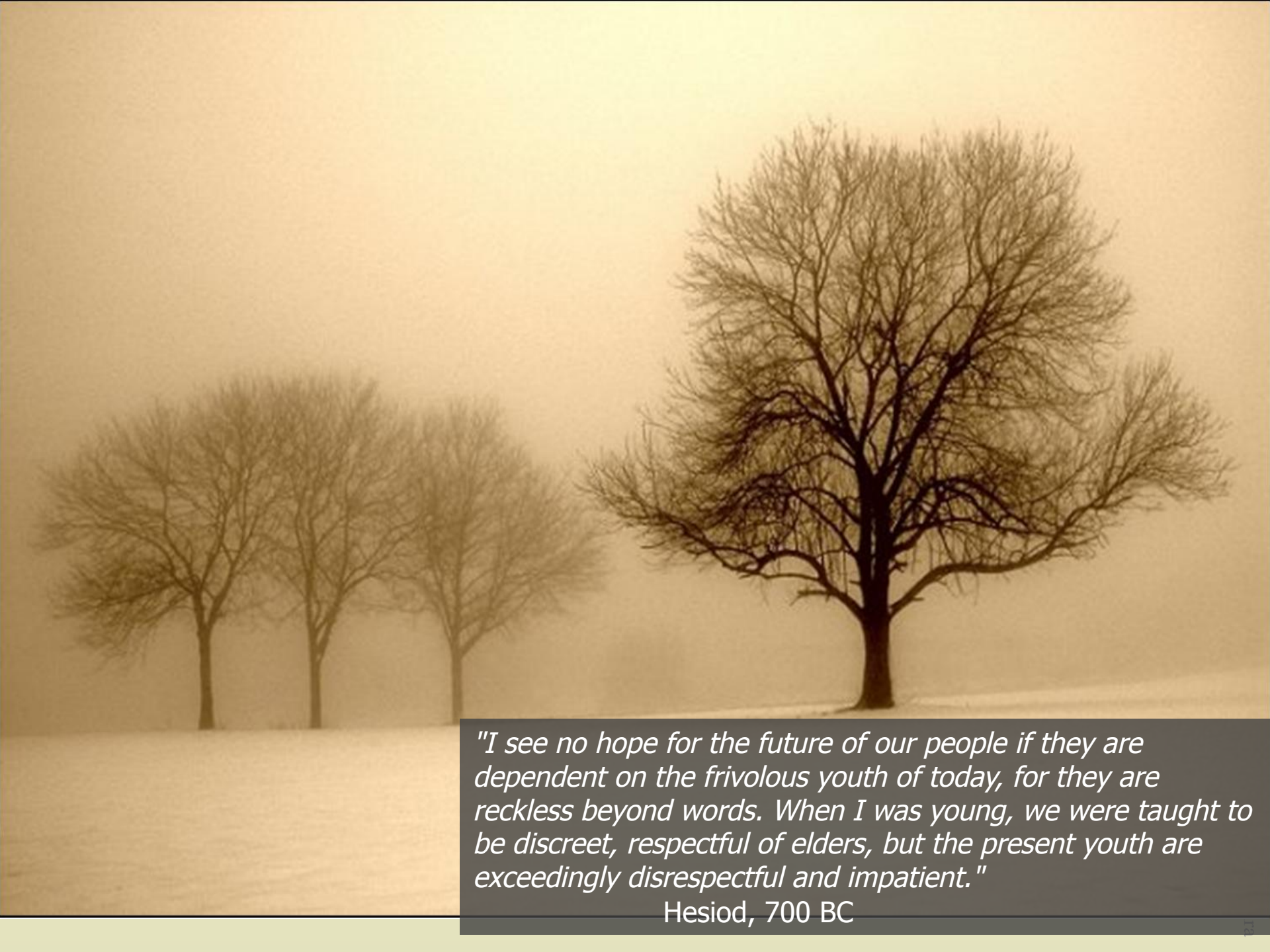
Singer. Plos Med 2005. e167

Duration of Antimicrobial Activity

Reduction of exposure

Siegel et al (1999, [10])	Cefuroxime 750mg q8h IV, 2d, then cefuroxime axetil 500mg q12 PO, 5d, 7d in total	Cefuroxime 750mg q8h IV, 2d, then cefuroxime axetil 500mg q12 PO, 8d, 10d in total	52	No difference in clinical cure
Leophonte et al (2002, [11])	Ceftriaxone 1g IV qd, 5d	Ceftriaxone 1g IV qd, 10d	244	No difference in clinical cure
Dunbar et al (2003, [12])	Levofloxacin 750mg IV/PO qd, 5d	Levofloxacin 500mg IV/PO qd, 10d	528	No difference in clinical cure and bacteriological outcome
Dunbar et al (2004, [13])	Levofloxacin	Levofloxacin 500mg IV/PO qd,	149	Noninferiority in l cure and riological me
Leophonte et al (2004, [14])				erence in l, bacteriological, and radiological efficacy
Tellier et al (2004, [15])	Telithromycin 800mg PO qd, 5d	Telithromycin 800mg PO qd, 7d	378	No difference in clinical cure and bacteriological outcome
Tellier et al (2004, [15])	Telithromycin 800mg PO qd, 5d or 7d	Clarithromycin 500mg PO bid, 10d	559	No difference in clinical cure and bacteriological outcome
El Moussaoui et al (2006, [16])	Amoxicillin 1g IV q6h, 3d	Amoxicillin 1g IV q6h, 3d, then amoxicillin 750mg PO q8h, 5d, 8d in total	119	Noninferiority in clinical and radiological success
File et al (2007, [17])	Gemifloxacin 320mg PO qd, 5d	Gemifloxacin 320mg PO qd, 7d	510	Non-inferiority in clinical, bacteriological, and radiological efficacy

3-7 d vs. 7-10 d
No difference in outcomes


"I see no hope for the future of our people if they are dependent on the frivolous youth of today, for they are reckless beyond words. When I was young, we were taught to be discreet, respectful of elders, but the present youth are exceedingly disrespectful and impatient."
Hesiod, 700 BC