



Traduzindo conceitos para as estratégias de dose

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Conflitos de interesse

- Pfizer
- Astra-Zeneca
- Novartis
- MSD

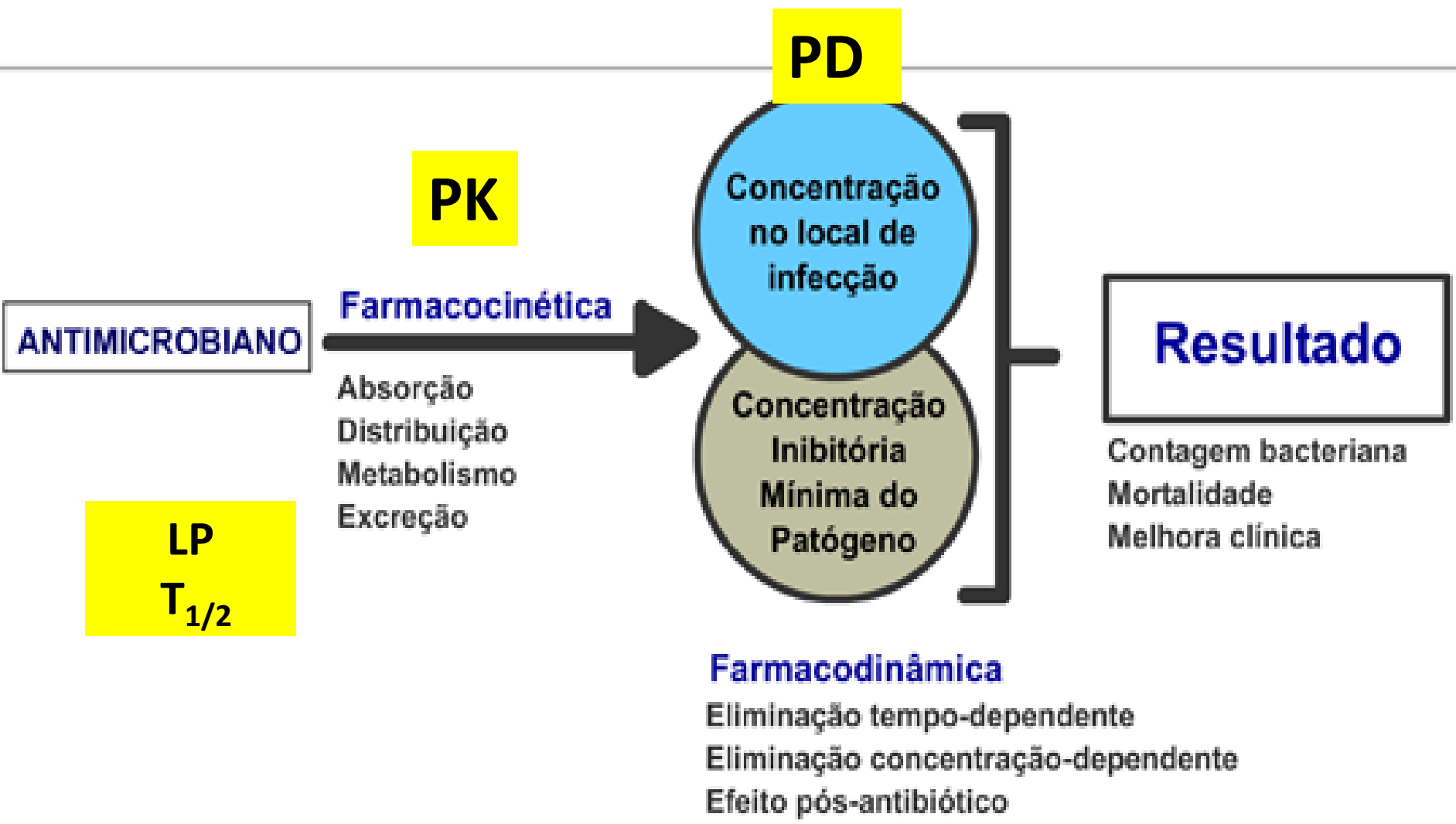
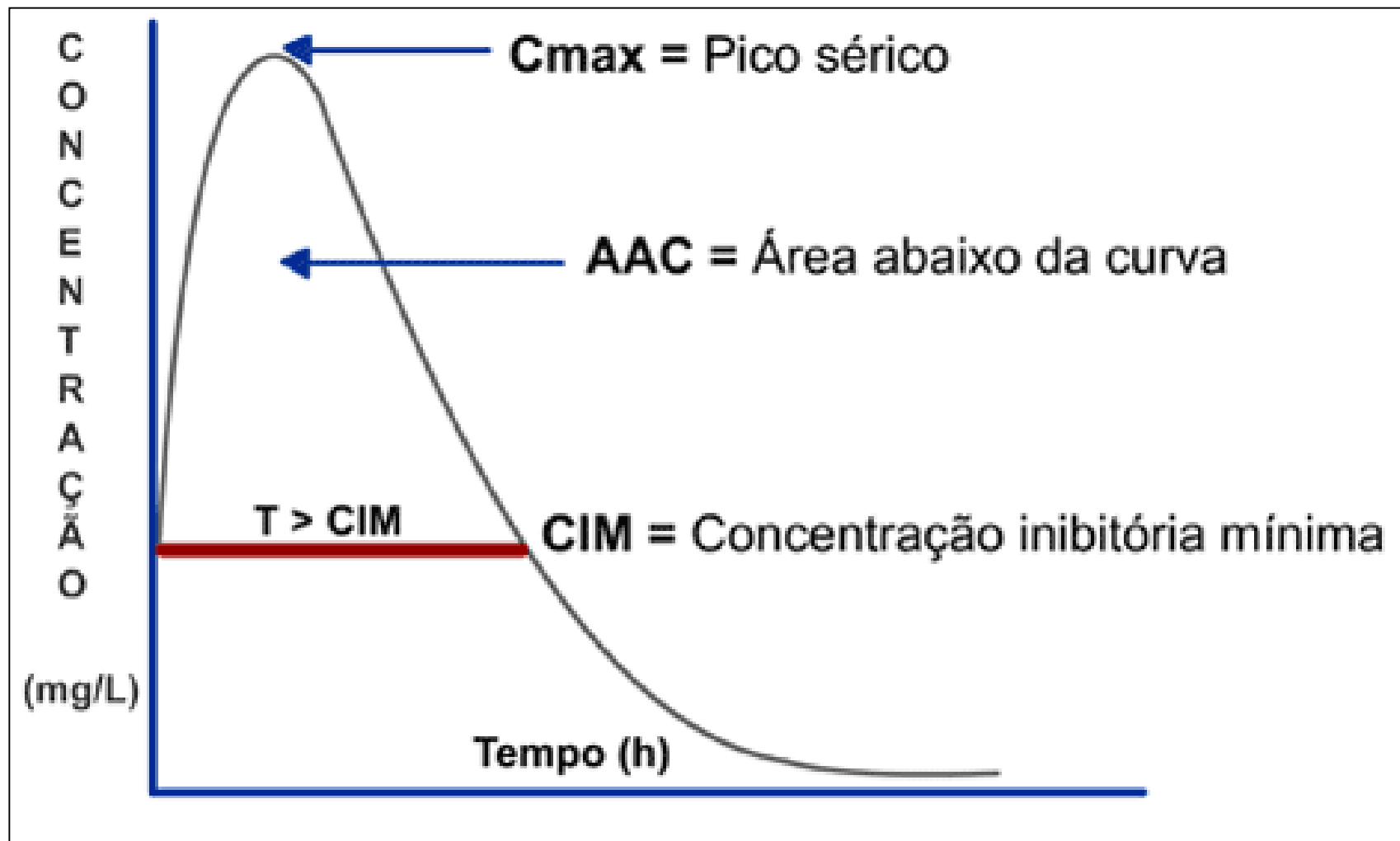


Figura 1. Fatores relacionados à ação dos antimicrobianos.

Otimização da terapia com ATM



Parâmetros Farmacodinâmicos – PD

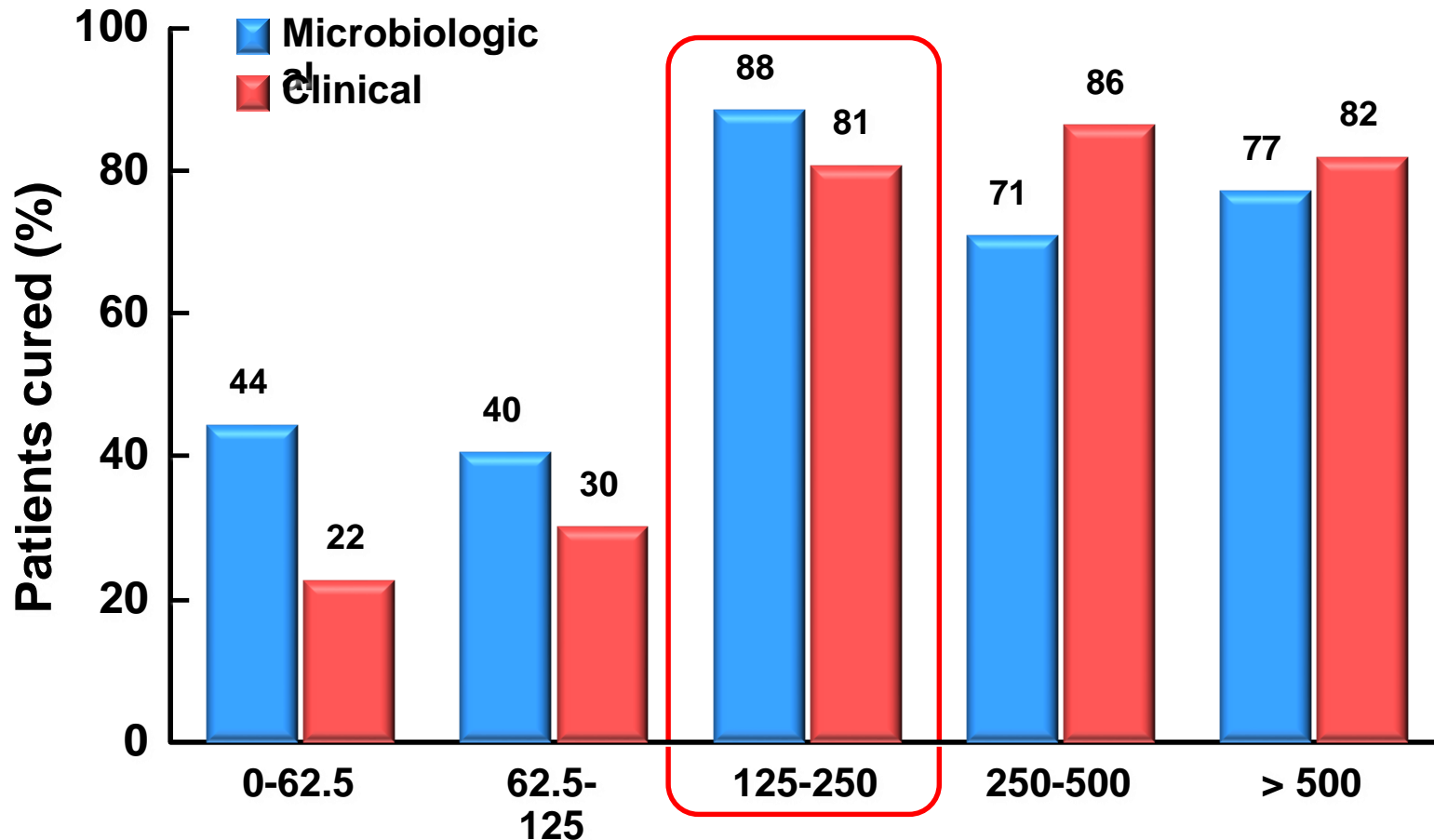
- Pico de concentração plasmática sobre MIC
(C_{max}/MIC)
- Tempo que a concentração excede a MIC
($\%T > MIC$)
- Área acima da curva sobre a MIC
- (AUC/MIC)

PD dos Antimicrobianos

DROGAS	CARACTERÍSTICA PD	PARÂMETROS ÓTIMOS PD
B-Lactâmicos Carbapenêmicos Linezolida Eritromicina Claritromicina Lincosamidas	Tempo-dependente	%T>MIC
Aminoglicosídeos Metronidazol Fluorquinolonas Telitromicina Daptomicina Quinopristina+Dalfopristina	Concentração-dependente	C _{max} /MIC
Fluorquinolonas Aminoglicosídeos Azitromicina Tetraciclina Glicopeptídeos Tigeciclina Quinopristina+Dalfopristina	Concentração-dependente com tempo-dependência	AUC/MIC

Fluoroquinolones

AUC:MIC

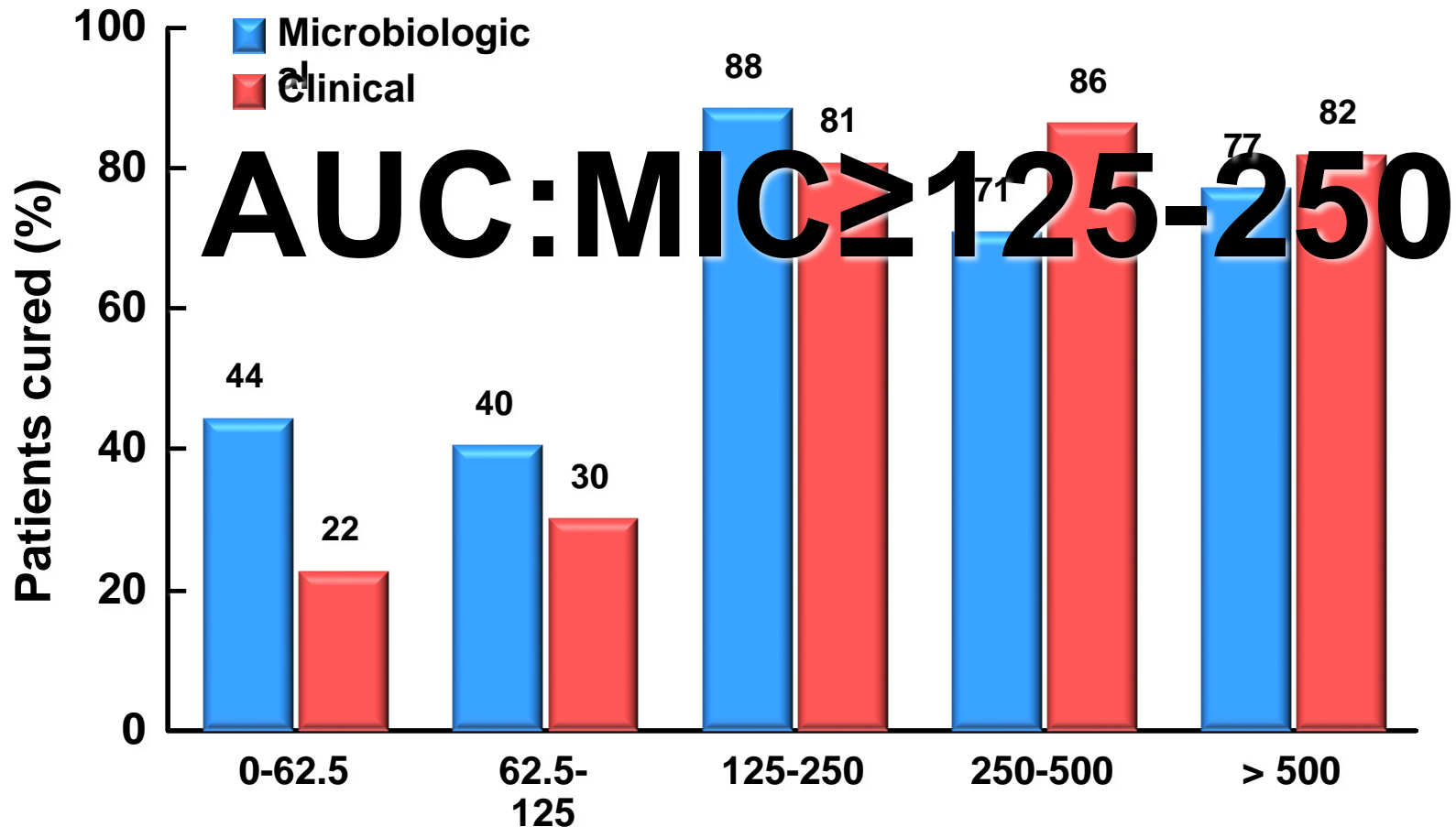


Forrest A et al. Antimicrob Agents Chemother 1993;37:1073-1081

Zelenitsky & Ariano J Antimicrob Chemother 2010;65:1725-32

Peloquin et al, Arch Intern Med 1989;149:2269-73

Fluoroquinolones

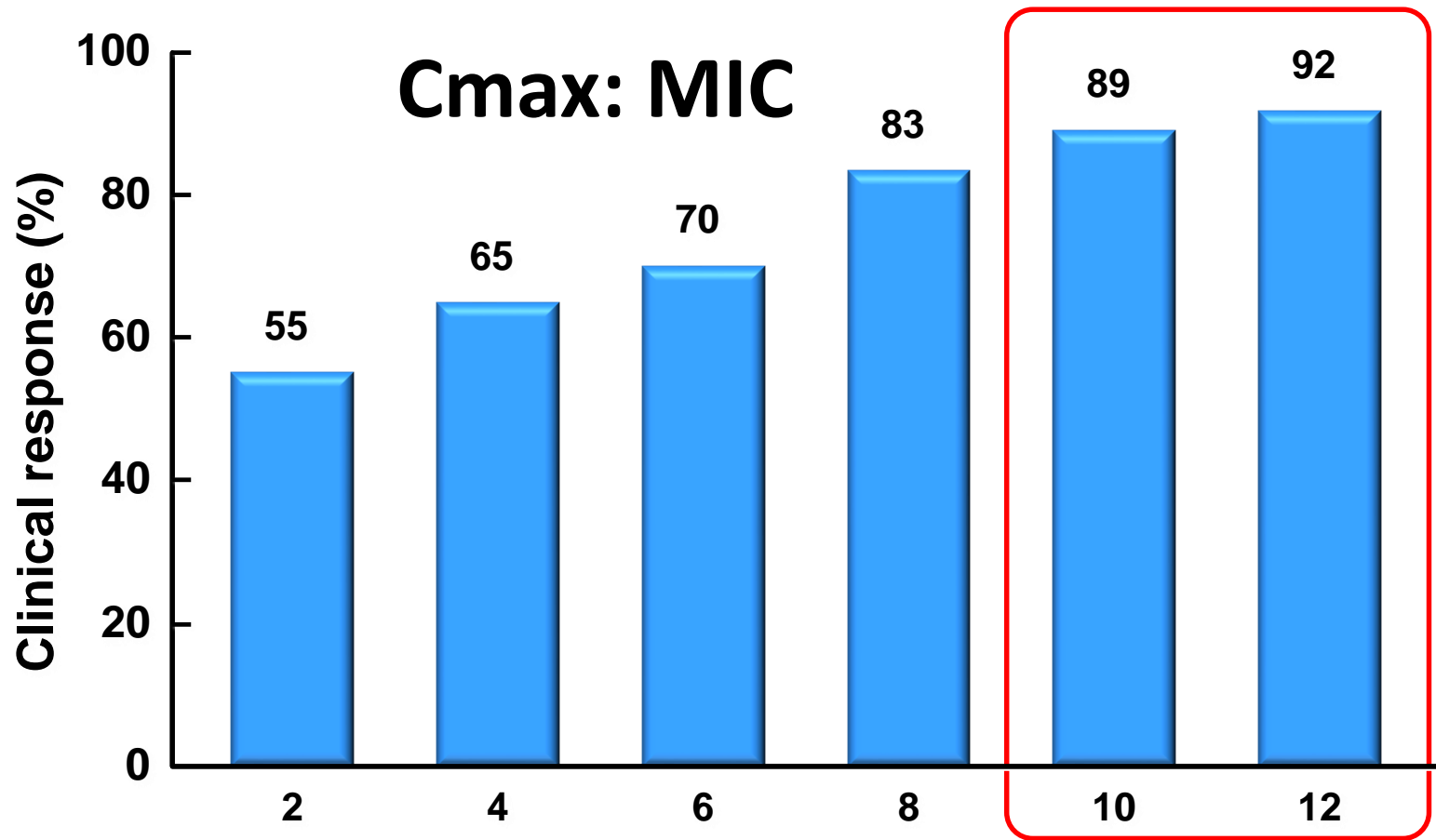


Forrest A et al. Antimicrob Agents Chemother 1993;37:1073-1081

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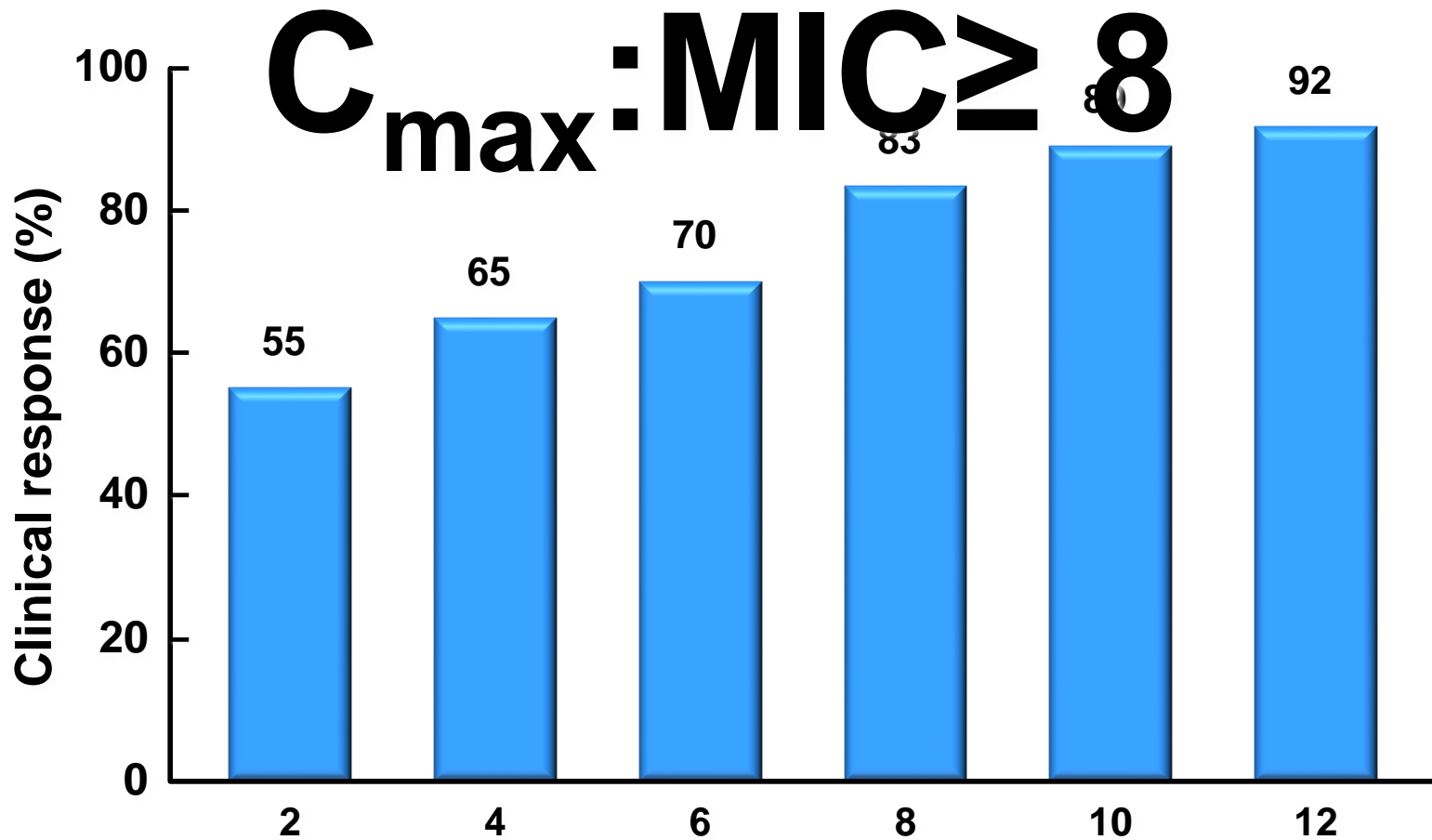
Peloquin et al, Arch Intern Med 1989;149:2269-73

Aminoglycosides



Moore et al., J Infect Dis 1987;155:93-99
Drusano et al, Clin Infect Dis 2007;45:753-60

Aminoglycosides



Moore et al., *J Infect Dis* 1987;155:93-99
Drusano et al, *Clin Infect Dis* 2007;45:753-60

Vancomicina

- Cura Clínica e microbiológica

AUC:MIC \geq 400-450

Moise-Broder et al, Clin Pharmacokinet 2004;43:925-42

Zelenitsky et al Int J Antimicrob Agents 2013;41:255-60

Linezolida

- Cura Clínica e microbiológica

AUC:MIC \geq 80-120

T>MIC 85%

Tigeciclina

- Cura Clínica e microbiológica

AUC:MIC \geq 6.9-17.9 (12.8-17.9)

Meagher et al, Diagn Microbiol Infect Dis 2005;52:165-71

Bhavnani et al Antimicrob Agents Chemother 2012;56:1065-72

Meagher et al Clin Infect Dis 2005; 41(suppl5): S333-40

Dr. Harry Eagle (1905-1992)

Eagle H et al. The effective concentrations of penicillin in vitro and in vivo for streptococci, pneumococci, and Treponema pallidum. *J*

Bacteriol 1950;59:625-43

Eagle H et al. Effect of schedule of administration on the therapeutic efficacy of penicillin; importance of the aggregate time penicillin remains at effectively bactericidal levels. *Am J Med*

1950;9:280-99

Eagle H et al. Continuous vs. Discontinuous therapy with penicillin: the effect of the interval between injections on therapeutic efficacy. *N*

England J Med 1953;248:481-8

β -Lactâmicos

- Concentração droga livre deve exceder o MIC para efeito **bacteriostático / bactericida**

Cefalosporinas 35 a 40% / 60 a 70%

Penicilinas 30% / 50%

Carbapenêmicos 20% / 40%

Idealmente 4-5x o MIC

β -Lactâmicos

- Concentração livre de β -lactâmicos deve ser superior ao MIC para efeito bactericida

Cefalosporinas

60 a 70%

Penicilinas

50%

Carbapenems

50%

Idealmente 4-5x o MIC

β -Lactâmicos

- **T > MIC**

Cefalosporinas

fT > 100% MIC

Penicilinas

4-5x o MIC

Carbapenêmicos

Roberts JA et al IJAA 2010;36:332-339

Udy AA Chest 2012;142:30-39

Aubert G et al, Ther Drug Monit 2010;32:517-519

Roberts JA et al, Int J Antimicrob Agents 2010;36:332-339

Blondiaux N et al, Int J Antimicrob Agents 2010;35:500-503

Taccone FS et al, Antimicrob Agents Chemother 2012;56:2129-31

Patel et al Ther Drug Monit 2012;34:160-164

Métodos para Aumentar % T > MIC

- Aumentar a potência *in vitro* (Atb)
- Aumentar a dose
- Reduzir intervalo entre as doses
- Aumentar duração da infusão
 - Infusão prolongada
 - Infusão contínua

Métodos para Aumentar % T > MIC

- Reduzir intervalo entre as doses
- Aumentar duração da infusão
 - Infusão prolongada
 - Infusão contínua

Reduzir intervalo entre doses

- Ex:

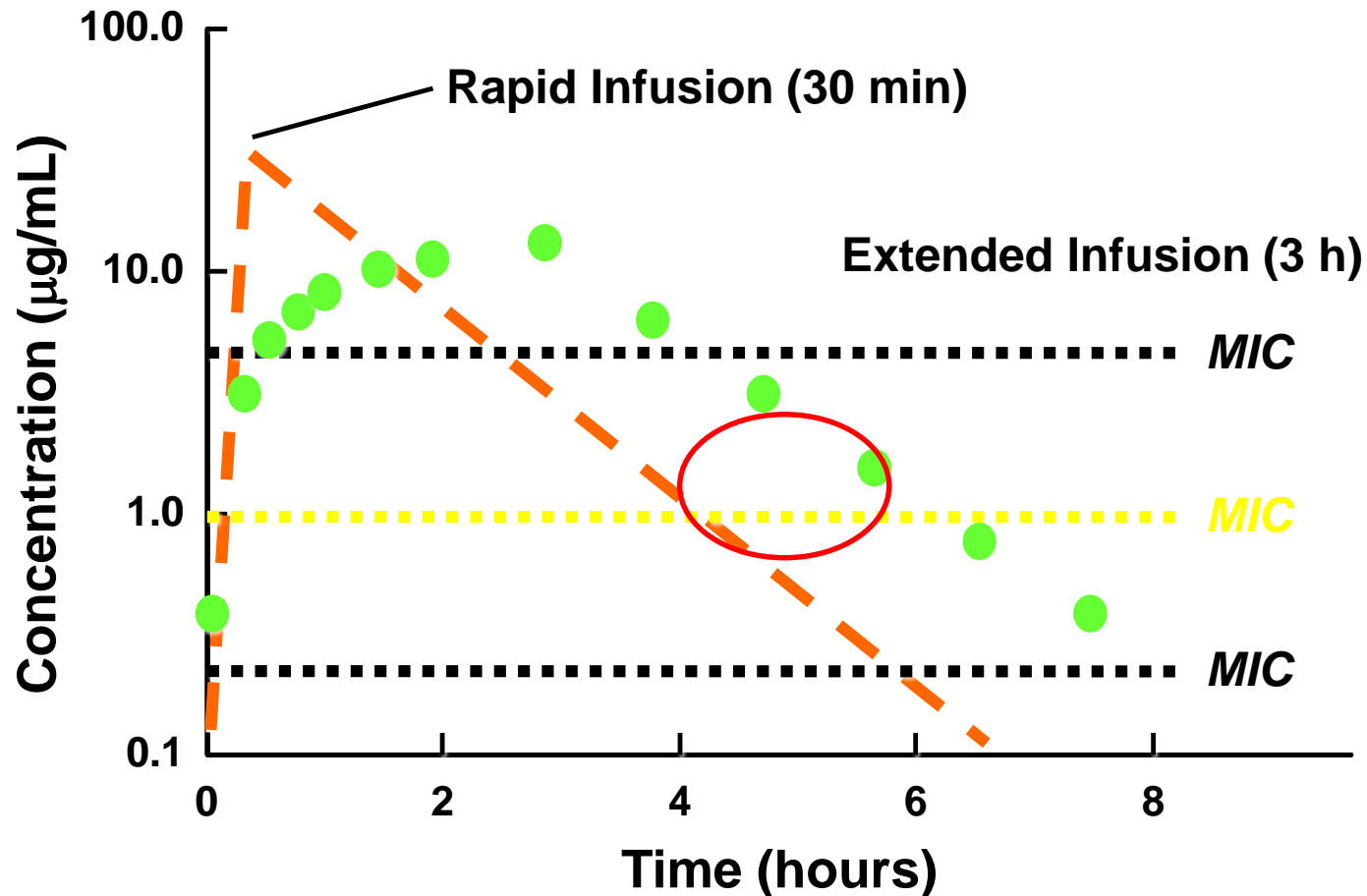
Cefepime 1g q6h (**$T_{1/2}=2h$**)

Meropenem 1g q6h ou 1.5g q6h (**$T_{1/2}=1h$**)

Ceftazidima 1g q6h ou 1.5g q6h (**$T_{1/2}=1.9h$**)

Extended Infusion

Meropenem 500mg Administered as a 0.5-Hour or 3-Hour Infusion



Concentração Sérica, cont.vs rápida

Antibiotic	Mean Cmin	Mean Css	Css/Cmin
• Ceftazidime	19	47	2.4
• Ceftazidime	25	30	1.2
• Ceftazidime	4	19	4.8
• Ceftazidime	≈5	40	8
• Ceftazidime	19	63	3.3
• Cefepime	5	41	8.2
• Piperacillin	5	18	3.6

Buijk et al, J Antimicrob Chemother 2002;49:121-8; Benko et al, Antimicrob Agents Chemother 1996;40:691-5; Hanes et al, Am J Surg 2000;179:436-40; Alou et al, J Antimicrob Chemother 2005;55:209-13; Lipman et al, J Antimicrob Chemother 1999;43:309-11; Young et al, J Antimicrob Chemother 1997;40:269-73; Jaruratanasirikul et al, J Pharm Pharmacol 2002;54:1693-6; Roberts et al, SHPA;2006

Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

Joel M. Dulhunty,¹ Jason A. Roberts,¹ Joshua S. Davis,² Steven A. R. Webb,³ Rinaldo Bellomo,⁴ Charles Gomersall,⁵ Charudatt Shirwadkar,⁶ Glenn M. Eastwood,⁴ John Myburgh,⁷ David L. Paterson,⁸ and Jeffrey Lipman¹

¹Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, and Burns, Trauma and Critical Care Research Centre, University of Queensland, Brisbane, ²Menzies School of Health Research, Charles Darwin University and Royal Darwin Hospital, ³Royal Perth Hospital, and School of Medicine and Pharmacology, University of Western Australia, Perth, ⁴Department of Intensive Care, Austin Hospital, Melbourne, Australia; ⁵Prince of Wales Hospital and Chinese University of Hong Kong, Hong Kong; ⁶Blacktown Hospital, ⁷Critical Care and Trauma Division, George Institute for Global Health, Sydney, and ⁸Infectious Diseases Unit, Royal Brisbane and Women's Hospital, and University of Queensland Centre for Clinical Research, Brisbane, Australia

(See the Editorial Commentary by Drusano and Lodise, on pages 245–7, and the Invited Article by Falagas et al, on pages 272–82.)

Dulhunty et al, CID 2013;56:236-44

**Double blind, RCT Continuous infusion vs.
Intermittent infusion in severe sepsis**

- PTZ,TCL e MEM
- AUS e Hong Kong
- 60 ptes (30 vs. 30)
- Infusão contínua:
 - **Melhor concentração sérica vale (81.8% vs 28.6%,
p=0.01)**
 - **Maior cura clínica (70 vs. 43%, p=0.03)**
 - **Sem diferenças em sobrevivência hospitalar e dias
fora da UTI**

Ellie J. C. Goldstein, Section Editor

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

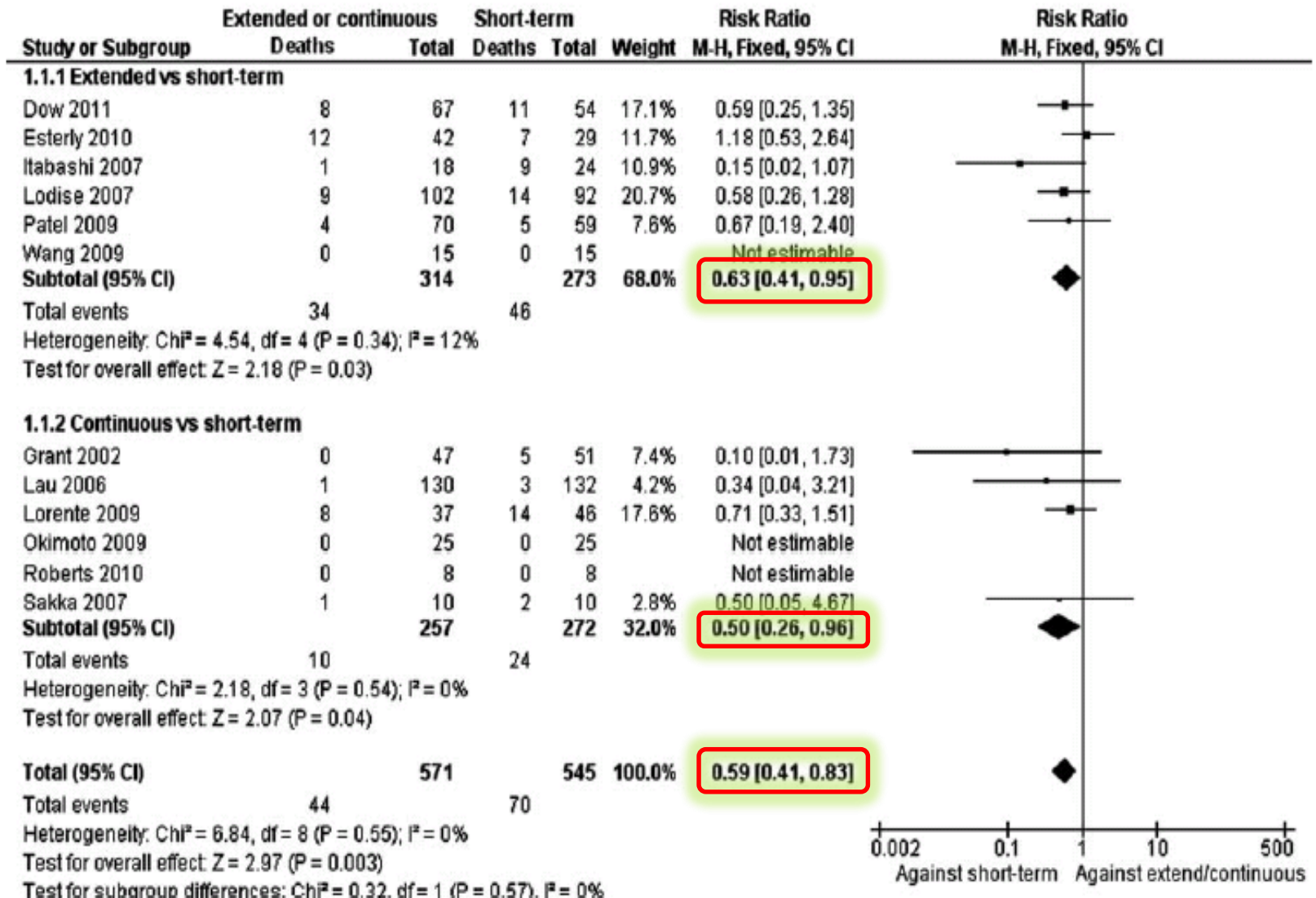
Matthew E. Falagas,^{1,2,4} Giannoula S. Tansarli,¹ Kazuro Ikawa,³ and Konstantinos Z. Vardakas^{1,2}

¹Alfa Institute of Biomedical Sciences (AIBS), ²Department of Internal Medicine-Infectious Diseases, Mitera Hospital, Hygeia Group, Athens, Greece;

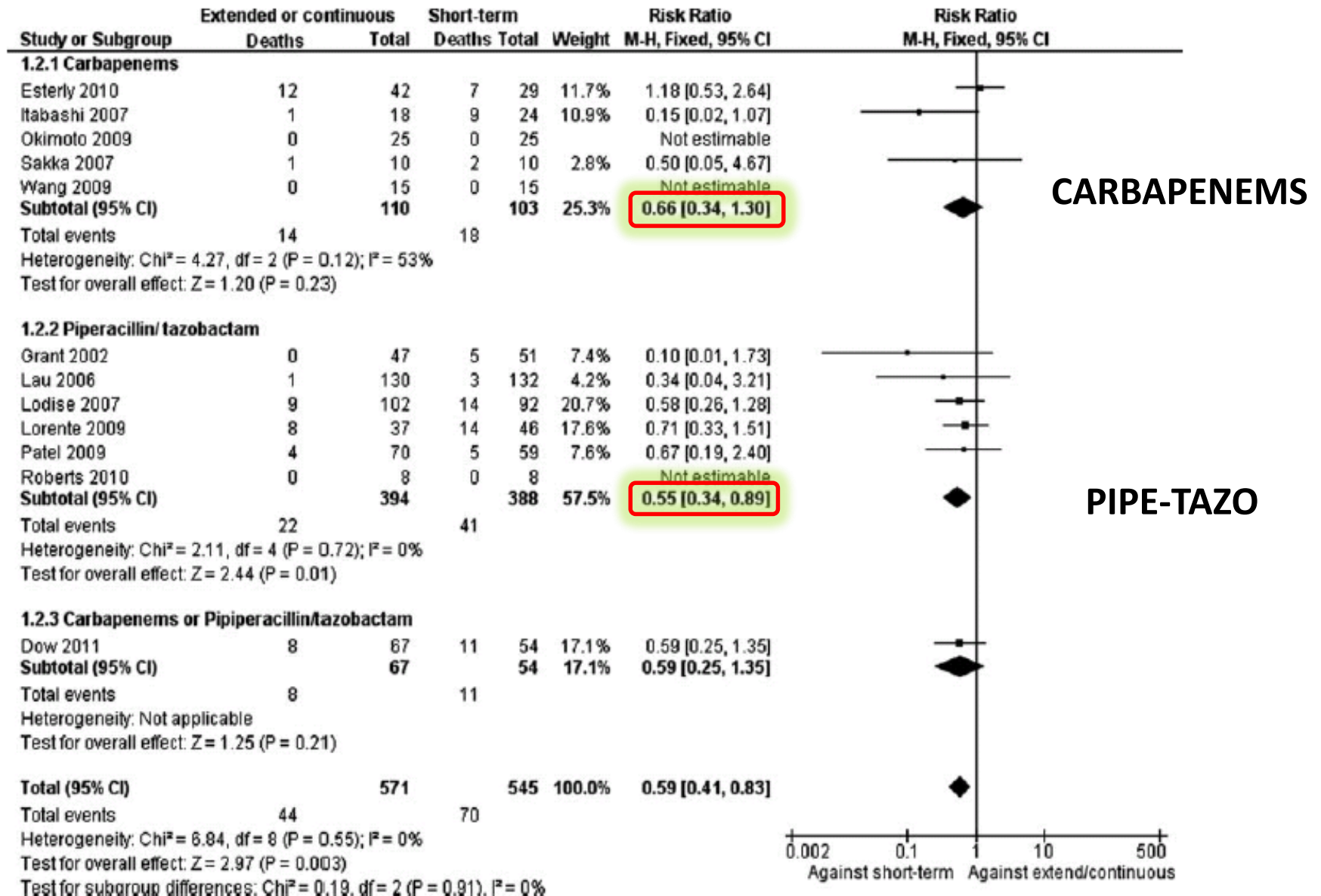
³Department of Clinical Pharmacotherapy, Hiroshima University, Japan; and ⁴Tufts University School of Medicine, Boston, Massachusetts

(See the Major Article by Dulhunty et al, on pages 236–44, and the Editorial Commentary by Drusano and Lodise, on pages 245–7.)

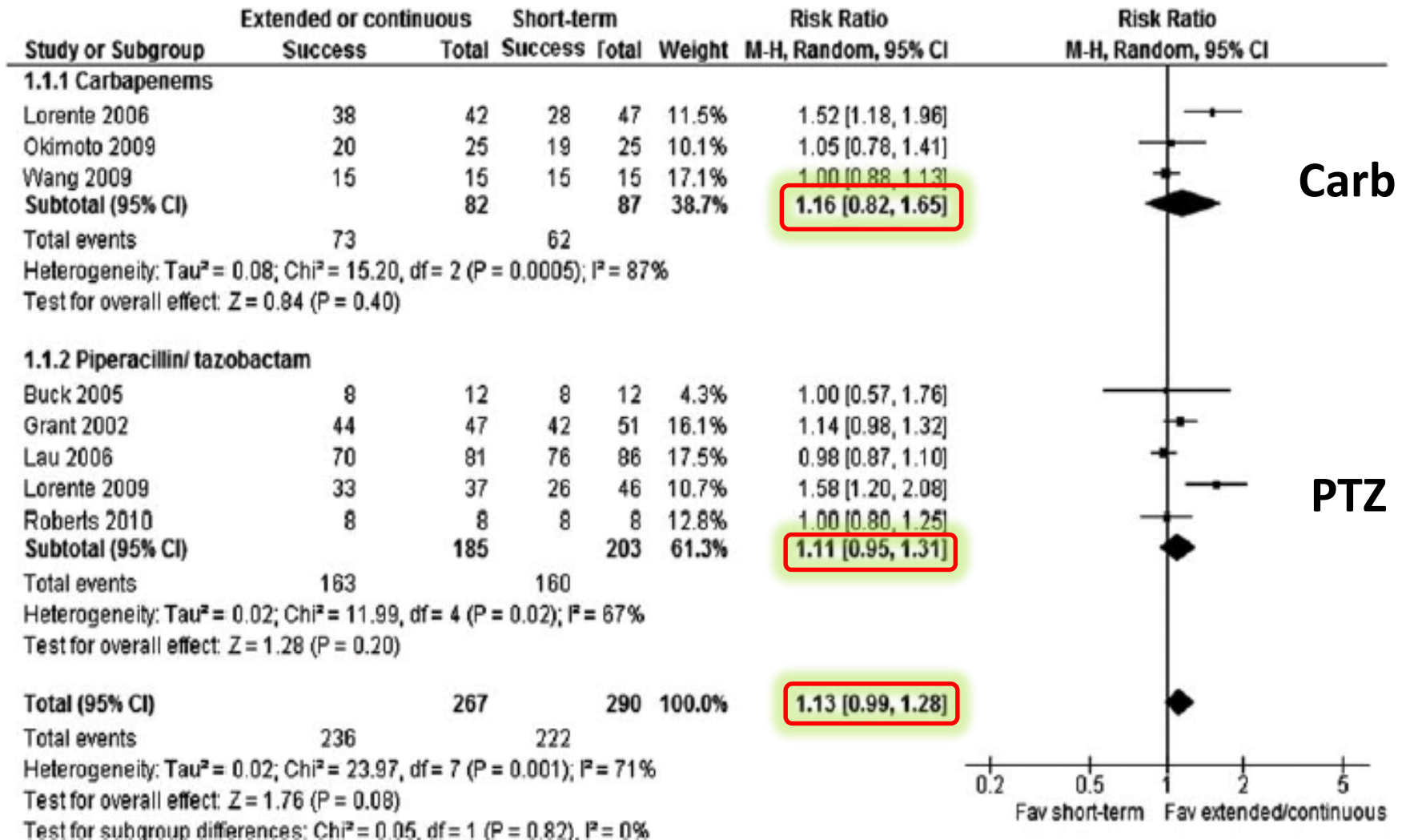
Mortalidade



Mortalidade por antibiótico

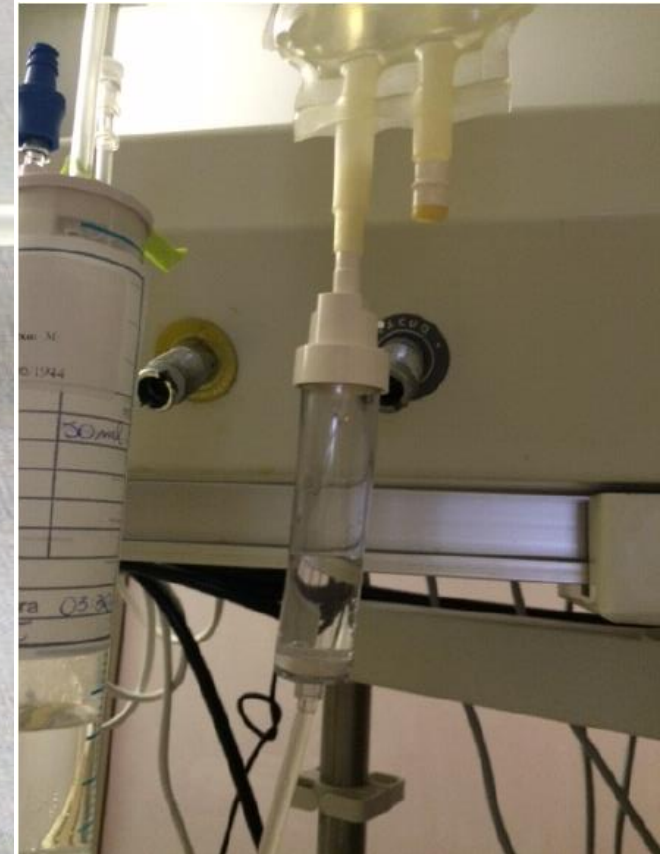


Cura clínica





Equipo de Infusão Prolongada



Por outro lado?

ARNOLD et al, Ann Pharmacotherapy 2013;47:170-80

Prolonged infusion antibiotics for suspected gram-negative infections in the ICU: a before-after study

- 503 ptes (242 II vs. 261 IP)
- MEM/TZP/FEP
- Infusão contínua:
 - Sucesso clínico (56.6% II vs. 51% IP, $p=0.20$)
 - Sucesso microbiológico (55.2% II vs. 49.5% IP, $p=0.48$)
 - Mortalidade 14 dias (13.2% II vs. 18% IP, $p=0.14$)
 - Mortalidade 30 dias (23.6% II vs. 25.7% IP, $p=0.58$)
 - Mortalidade hospitalar (19.4% II vs. 23% IP, $p=0.32$)

Extended-Infusion versus Standard-Infusion Piperacillin-Tazobactam for Sepsis Syndromes at a Tertiary Medical Center

Scott R. Cutro,^{a*} Robert Holzman,^a Yanina Dubrovskaya,^b Xian Jie Cindy Chen,^b Tanla Ahuja,^b Marco R. Scipione,^b Donald Chen,^a John Papadopoulos,^b Michael S. Phillips,^a Sapna A. Mehta^a

Division of Infectious Diseases, New York University School of Medicine, New York, New York, USA^a; Department of Pharmacy, New York University-Langone Medical Center, New York, New York, USA^b

Piperacillin-tazobactam (PTZ) is frequently used as empirical and targeted therapy for Gram-negative sepsis. Time-dependent killing properties of PTZ support the use of extended-infusion (EI) dosing; however, studies have shown inconsistent benefits of EI PTZ treatment on clinical outcomes. We performed a retrospective cohort study of adult patients who received EI PTZ treatment and historical controls who received standard-infusion (SI) PTZ treatment for presumed sepsis syndromes. Data on mortality rates, clinical outcomes, length of stay (LOS), and disease severity were obtained. A total of 843 patients (662 with EI treatment and 181 with SI treatment) were available for analysis. Baseline characteristics of the two groups were similar, except for fewer female patients receiving EI treatment. No significant differences between the EI and SI groups in inpatient mortality rates (10.9% versus 13.8%; $P = 0.282$), overall LOS (10 versus 12 days; $P = 0.171$), intensive care unit (ICU) LOS (7 versus 6 days; $P = 0.061$), or clinical failure rates (18.4% versus 19.9%; $P = 0.756$) were observed. However, the duration of PTZ therapy was shorter in the EI group (5 versus 6 days; $P < 0.001$). Among ICU patients, no significant differences in outcomes between the EI and SI groups were observed. Patients with urinary or intra-abdominal infections had lower mortality and clinical failure rates when receiving EI PTZ treatment. We did not observe significant differences in inpatient mortality rates, overall LOS, ICU LOS, or clinical failure rates between patients receiving EI PTZ treatment and patients receiving SI PTZ treatment. Patients receiving EI PTZ treatment had a shorter duration of PTZ therapy than did patients receiving SI treatment, and EI dosing may provide cost savings to hospitals.

662 pacientes com infusão estendida

Patient group and outcome	EI PTZ	SI PTZ	<i>P</i>
All patients			
Total no.	662	181	
Death (no. [%])	72 (10.9)	25 (13.8)	0.282
Mean LOS (days [median])	14.9 (10)	15.0 (12)	0.171
Mean duration of PTZ treatment (days [median])	5.8 (5)	6.8 (6)	<0.001 ^a
Clinical failure (no. [%])	122 (18.4)	36 (19.9)	0.756

Patient group, source of infection, and outcome	No. of indicated outcome/ total no. (%)		<i>P</i>
	EI PTZ	SI PTZ	
All patients			
Pulmonary			
Death	53/371 (14.3)	10/95 (10.5)	0.403
Clinical failure	90/371 (24.3)	16/95 (16.8)	0.168
Urinary			
Death	2/80 (2.5)	5/30 (16.7)	0.016 ^a
Clinical failure	5/80 (6.3)	8/30 (26.7)	0.006 ^a
Intra-abdominal			
Death	8/110 (7.3)	6/32 (18.8)	0.086
Clinical failure	16/110 (14.5)	8/32 (25.0)	0.184
Skin and soft tissue			
Death	6/62 (9.7)	3/16 (18.8)	0.380
Clinical failure	9/62 (14.5)	2/16 (12.5)	1

IMPACTO DA INFUSÃO PROLONGADA DE ANTIMICROBIANOS BETA- LACTÂMICOS NA MORBIDADE E MORTALIDADE DE PACIENTES CRÍTICOS

Defesa de Dissertação de Mestrado

Pós-graduando: Rodrigo Spinati Macedo

Orientador: Prof. Dr. Guilherme Furtado

EPM- UNIFESP 2014

Resultados

106 pacientes apresentaram critérios de inclusão



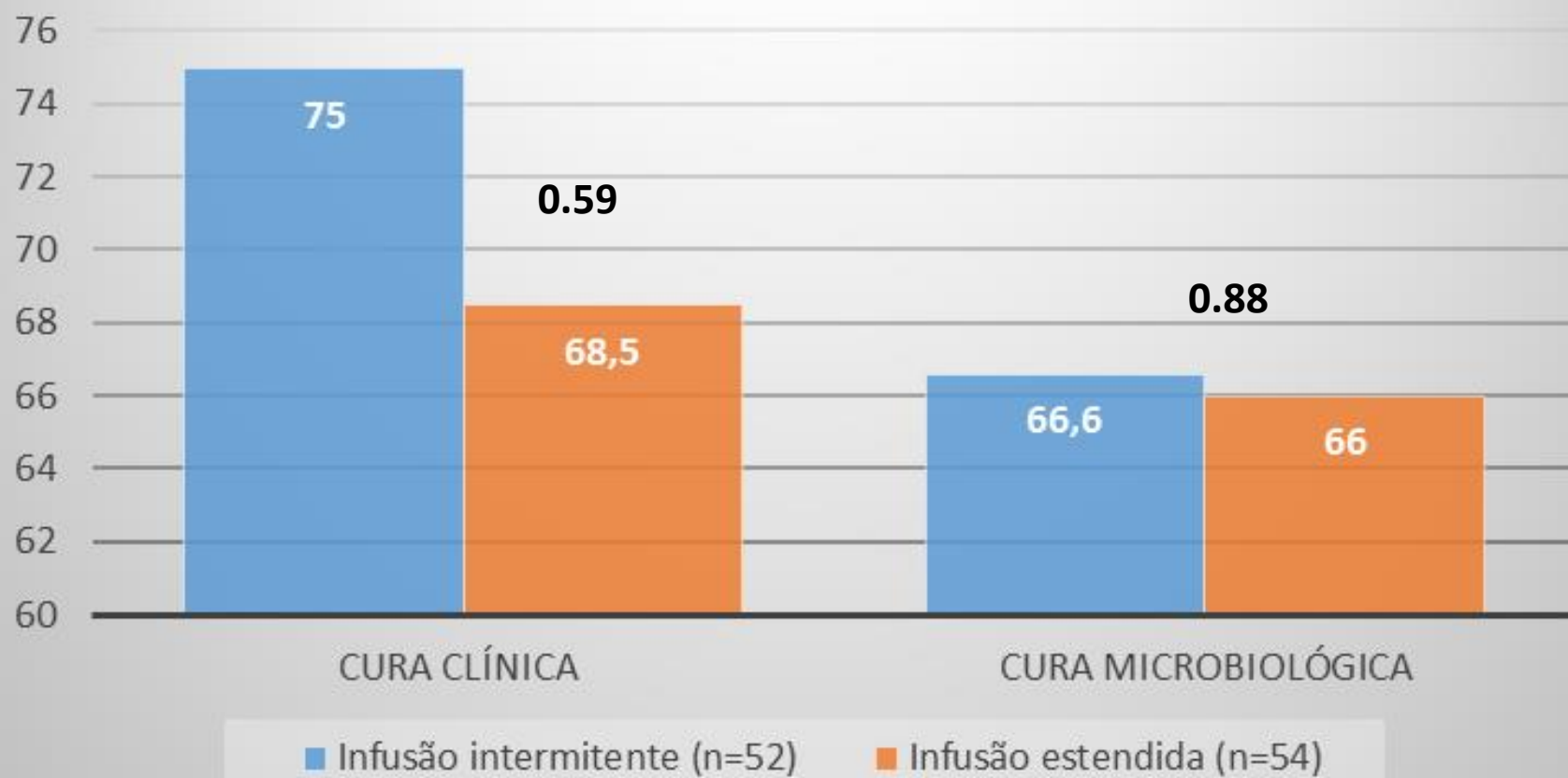
**52 pacientes (Grupo II)
(49,1%)**



**54 pacientes (Grupo IE)
(50,9%)**

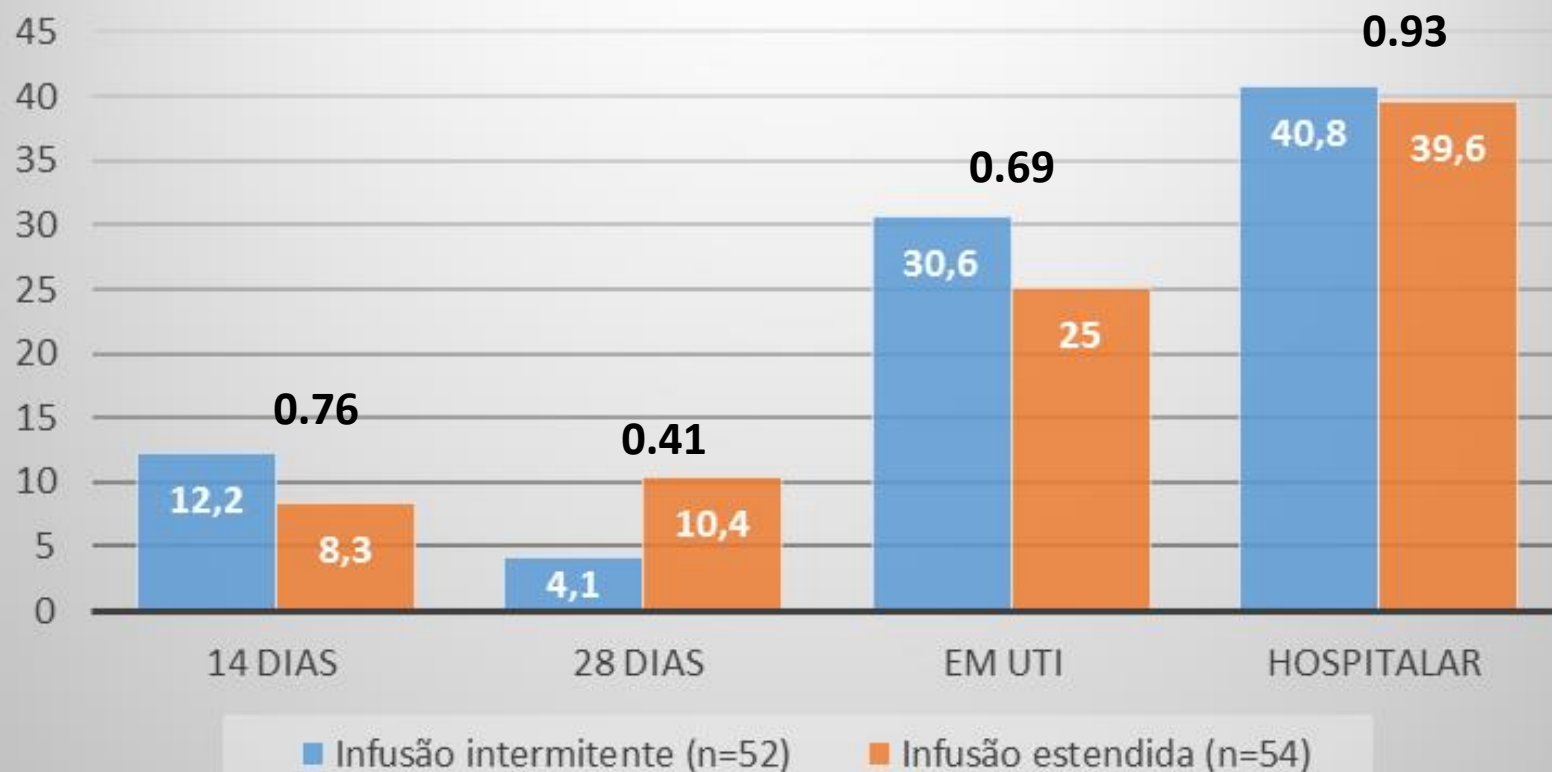
Resultados

Taxas de cura (%)



Resultados

Taxas de mortalidade (%)



Leandro dos Santos Maciel Cardinal

Dissertação apresentada à
Universidade Federal de São Paulo
– Escola Paulista de Medicina para
obtenção do título de Mestre em
Ciências.

Orientador: Prof. Dr. Guilherme Henrique Campos Furtado

**ANÁLISE DE DESFECHOS CLÍNICOS, ADEQUAÇÃO DA
TERAPIA ANTIMICROBIANA E DETERMINAÇÃO DA
FARMACODINÂMICA DE BETA-LACTÂMICOS EM PACIENTES
COM INFECÇÃO DE CORRENTE SANGUÍNEA POR
*PSEUDOMONAS AERUGINOSA***

Probabilidade de atingir o alvo terapêutico com diferentes regimes

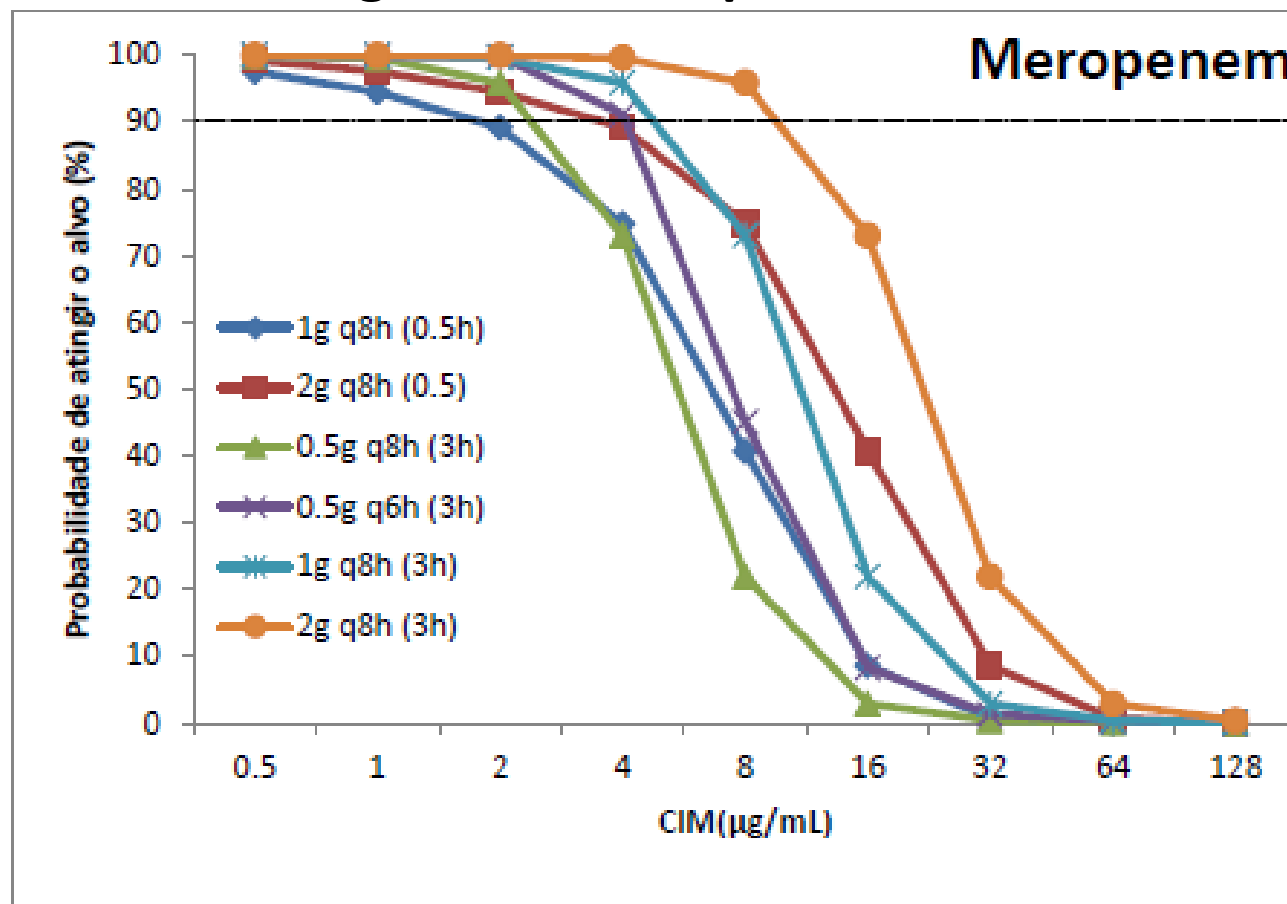


Figure 4. Probabilidade de atingir o alvo terapêutico com diferentes regimes de doses de meropenem com a meta estabelecida de 40% $fT > CIM$.

Probabilidade de atingir o alvo terapêutico com diferentes regimes

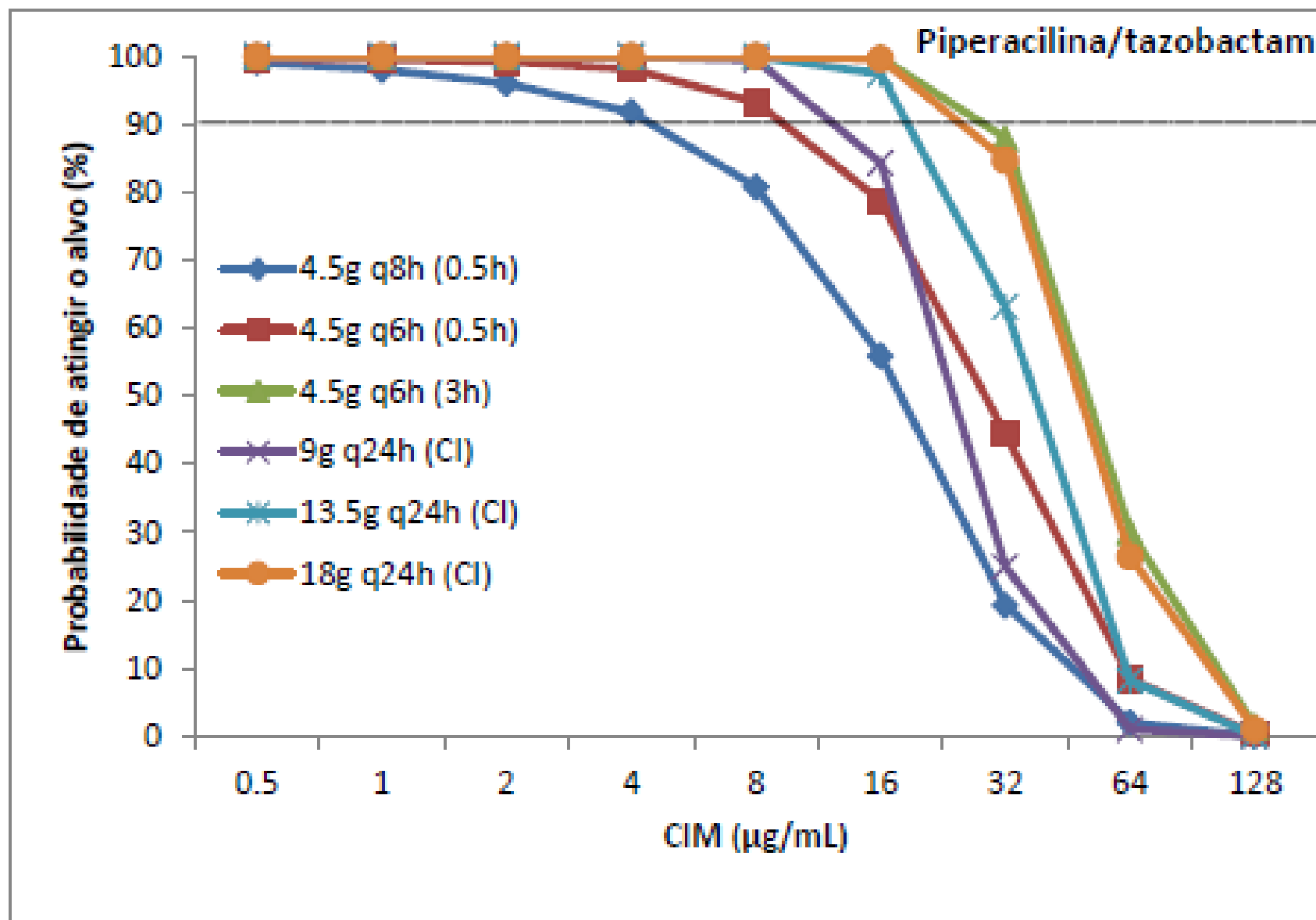


Tabela 15. Resultados da análise univariada da antibioticoterapia para mortalidade em 30 dias.

Variável	Óbito 30 dias	Não óbito 30 dias	P
Antibioticoterapia empírica			
Terapia empírica adequada	27/41 (65,9%)	20/37 (51,3%)	0,40
Monoterapia empírica	23/41 (56,1%)	27/37 (73,0%)	0,18
Terapia dupla empírica	14/41 (34,1%)	5/37 (13,5%)	0,06
Terapia tripla empírica	1/41 (2,4%)	0/37 (0%)	0,95
Terapia empírica otimizada com beta-lactâmico	7/25 (28%)	9/22 (40,9%)	0,53
Antibioticoterapia direcionada			
Terapia dirigida adequada	18/20 (90%)	28/34 (82,4%)	0,71
Monoterapia direcionada	10/19 (52,6%)	21/34 (61,8%)	0,72
Terapia dupla direcionada	9/19 (47,4%)	12/34 (35,3%)	0,56
Terapia tripla direcionada	0/19 (0%)	1/34 (2,9%)	0,76
Terapia direcionada otimizada com beta-lactâmico	3/8 (37,5%)	10/18 (55,6%)	0,67

Em suma

- Com EXCEÇÃO de Beta-lactâmicos, a posologia e modo de infusão não precisa ser mudada
- Maioria dos estudos clínicos em infusão prolongada sem significância em mortalidade, exceção:
Lodise et al, em Pipe-Tazo 0.5 vs 3h, menor mortalidade em ptes com APACHE II > 17
- Muitos com melhor resposta clínica, ex. cura clínica/microbiológica com vários beta-lactâmicos
- Ainda não há estudos analisando o impacto da TDM de BL em desfechos clínicos

“O difícil nós fazemos agora, o impossível leva um pouco mais de tempo”

David Ben Gurion

Primeiro-ministro Israelense

Obrigado

ghfurtado@gmail.com



**GRUPO DE DISCUSSÃO
DE ANTIMICROBIANOS EM DOENTES CRÍTICOS
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