



“IIª CONTROVÉRSIAS EM INFECÇÃO HOSPITALAR”

Era uma vez um dogma do tratamento de ESBL? Novos pontos de corte do CLSI e implicações em tratamento

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Como Era Realizada a Detecção de ESBL desde 2005

- Clinical and Laboratory Standards Institute
 - Critérios para *E. coli*, *K. pneumoniae*, *K. oxytoca* e *P. mirabilis*
 - Triagem com diâmetros dos halos de inibição ou MIC
- Teste confirmatório
 - Associações com inibidores de beta-lactamases
 - Diferentes perfis de especificidade e sensibilidade



Por que os pontos de corte foram revisados?

- Surgimento de novos mecanismos de resistência. Os pontos de corte foram estabelecidos antes do surgimento das ESBLs e pAmpC;
- Critérios de triagem estabelecidos somente para algumas espécies bacterianas;
- Maior conhecimento sobre pK/pD;
- A MIC é mais importante que o conhecimento do mecanismo de resistência?

Novos Pontos de Corte para Cefalosporinas e Aztreonam

Agente/	M100-S19 (2009) µg/mL			M10-S20 (2010) µg/mL			Regime
	S	I	R	S	I	R	
Aztreonam	≤8	16	≥32	≤4	8	≥16	
Cefazolina	≤8	16	≥32	≤1	2	≥4	1g 8/8h
Ceftriaxona	≤8	16-32	≥64	≤1	2	≥4	1g 24h
Cefotaxima	≤8	16-32	≥64	≤1	2	≥4	1g 8/8h
Ceftazidima	≤8	16	≥32	≤4	8	≥16	1g 8/8h
Cefepima	≤8	16	≥32	≤8	16	≥32	1g 8/8h ou 2g 12h

Não houve mudança dos pontos de corte para cefoxitina, cefotetan, cefuroxima parenteral e cefepima.

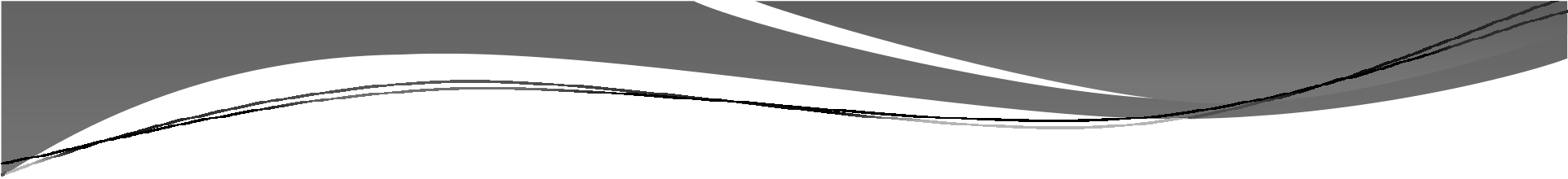
CLSI M100-S20. Table 2A.

Novos Pontos de Corte para Cefalosporinas e Aztreonam

Agente	M100-S19 (2009)			M10-S20 (2010)			Regime
	S	I	R	S	I	R	
Cefazolina	≥18	15-17	≤14	.*	.*	.*	1g 8/8h
Cefotaxima	≥23	15-22	≤14	≥26	23-25	≤22	1g 8/8h
Ceftriaxona	≥21	14-20	≤13	≥23	20-22	≤19	1g 24h
Ceftazidima	≥18	15-17	≤14	≥21	18-20	≤17	1g 8/8h
Aztreonam	≥22	16-21	≤15	≥21	18-20	≤17	1g 8/8h
Cefepima	≥18	15-17	≤14	≥18	15-17	≤14	1g 8/8h ou 2g 12h

*Pontos de Corte não estabelecidos

(7) Following evaluation of pharmacokinetics-pharmacodynamics (PK-PD) properties and limited clinical data, new (revised) interpretive criteria for cephalosporins (cefazolin, cefotaxime, ceftazidime, ceftizoxime, and ceftriaxone) and aztreonam were established and are listed in this table. Cefepime and cefuroxime (parenteral) were also evaluated; however, no change in interpretive criteria was required for the dosages indicated below. When using the new interpretive criteria, routine ESBL testing is no longer necessary before reporting results (eg, it is no longer necessary to edit results for cephalosporins, aztreonam, or penicillins from susceptible to resistant). However, until laboratories implement the new interpretive criteria, ESBL testing should be performed as described in Supplemental Table 2A-S1. ESBL testing may still be useful for epidemiological or infection control purposes.




Implicações Clínicas

Tratamento de ESBL

Outcome of Cephalosporin Treatment for Serious Infections Due to Apparently Susceptible Organisms Producing Extended-Spectrum β -Lactamases: Implications for the Clinical Microbiology Laboratory

DAVID L. PATERSON,^{1,2} WEN-CHIEN KO,³ ANNE VON GOTTBURG,⁴ JOSE MARIA CASELLAS,⁵
LUTFIYE MULAZIMOGLU,⁶ KEITH P. KLUGMAN,⁴ ROBERT A. BONOMO,⁷
LOUIS B. RICE,⁷ JOSEPH G. McCORMACK,² AND VICTOR L. YU^{1*}

TABLE 4. Outcome of serious infections due to ESBL-producing organisms is inferior when the MIC of antibiotics is 2 to 8 μ g/ml

MIC (μ g/ml)	% (no./total) of patients who:	
	Experienced failure of cephalosporin therapy	Died within 14 days of bacteremia
 8	100 (6/6)	33 (2/6)
4	67 (2/3)	0 (0/3)
2	33 (1/3)	0 (0/3)
≤ 1	27 (3/11)	18 (2/11)
Total ^a	54 (15/28)	

^a Includes five patients with whose isolates for which MICs were recorded simply as 0.5 to 4 mg/liter.

Extended-Spectrum β -Lactamases: a Clinical Update

David L. Paterson^{1*} and Robert A. Bonomo²

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TABLE 3. Recommended treatment for infections with ESBL-producing organisms

Infection type	Therapy of choice	Second-line therapy
Urinary tract infection	Quinolone ^a	Amoxicillin/clavualante
Bacteremia	Carbapenem	Quinolone ^a
Hospital-acquired pneumonia	Carbapenem	Quinolone ^a
Intra-abdominal infection	Carbapenem	Quinolone ^a (plus metronidazole)
Meningitis	Meropenem	Intrathecal polymyxin B

^a If the organism is quinolone susceptible.

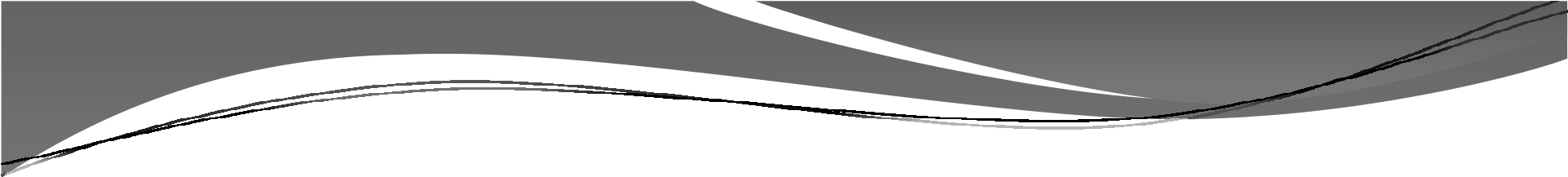
Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum β -lactamase-producing *Escherichia coli*

Cao Bin^a, Wang Hui^b, Zhu Renyuan^b, Ning Yongzhong^c, Xie Xiuli^b, Xu Yingchun^b,
Zhu Yuanjue^a, Chen Minjun^{b,*}

Table 1
Demographic characteristics and outcomes of 22 patients with bacteremia due to ceftazidime-susceptible *E. coli*

	Antibiotics after detection of bacteremia			<i>P</i>
	Ceftazidime	Imipenem/ cilastatin	Cefoperazone/ sulbactam	
Case no.	7	8	7	
Sex (M/F)	3/4	4/4	2/5	0.678
Underlying conditions, <i>n/N</i> (%)				
Malignancy	5/7 (71.4)	6/8 (75)	6/7 (85.7)	1.0
Neutropenia	1/7 (14.3)	2/8 (25)	0/7 (0)	–
Sources of bacteremia, <i>n/N</i> (%)				
Urinary	3/7 (42.8)	2/8 (25)	0/7 (0)	–
Biliary	1/7 (14.3)	2/8 (25)	5/7 (71.4)	0.649
Abdominal	1/7 (14.3)	1/8 (12.5)	1/7 (14.3)	0.602
Primary and others	2/7 (28.6)	3/8 (37.5)	1/7 (14.3)	0.602
Days in hospital (mean \pm SD)	17.1 \pm 21.4	39.5 \pm 44.1	25.3 \pm 32.5	0.744
APACHE II (mean \pm SD)	10.1 \pm 4.3	13.5 \pm 5.3	11.3 \pm 4.9	0.952
Outcomes, <i>n/N</i> (%)				
Success	6/7 (85.7)	7/8 (87.5)	5/7 (71.4)	0.637
Mortality	0/7 (0)	0/8 (0)	0/7 (0)	





**Posso prescrever cefepima
para o tratamento de
infecções causadas por
ESBL baseado nos
resultados de sensibilidade
propostos pelo CLSI?**

Cephalosporin MIC Distribution of Extended-Spectrum- β -Lactamase- and pAmpC-Producing *Escherichia coli* and *Klebsiella* Species[∇]

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Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology,¹ and Division of Infectious Diseases, Department of Medicine,² Mayo Clinic Rochester, Rochester, Minnesota

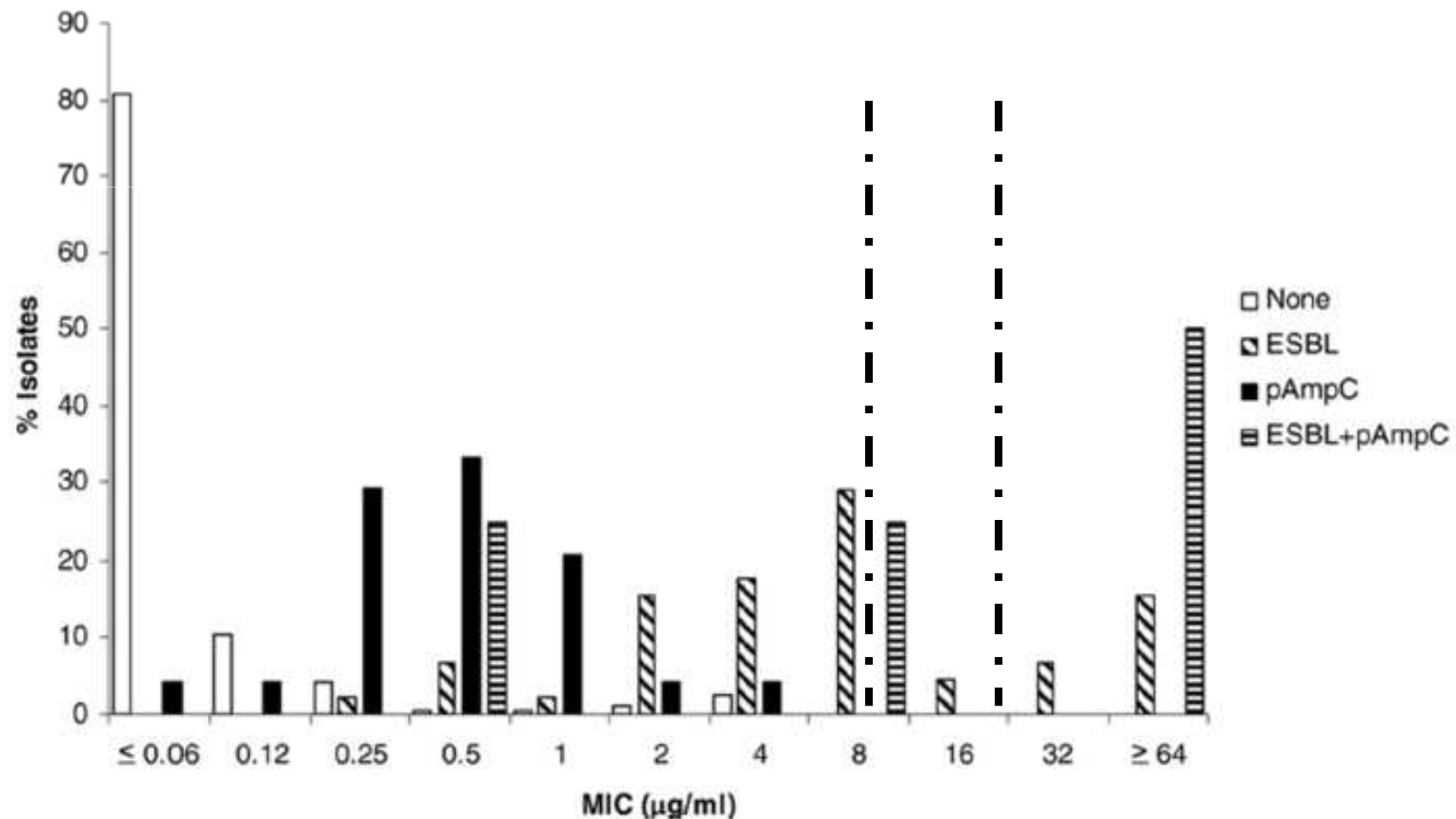
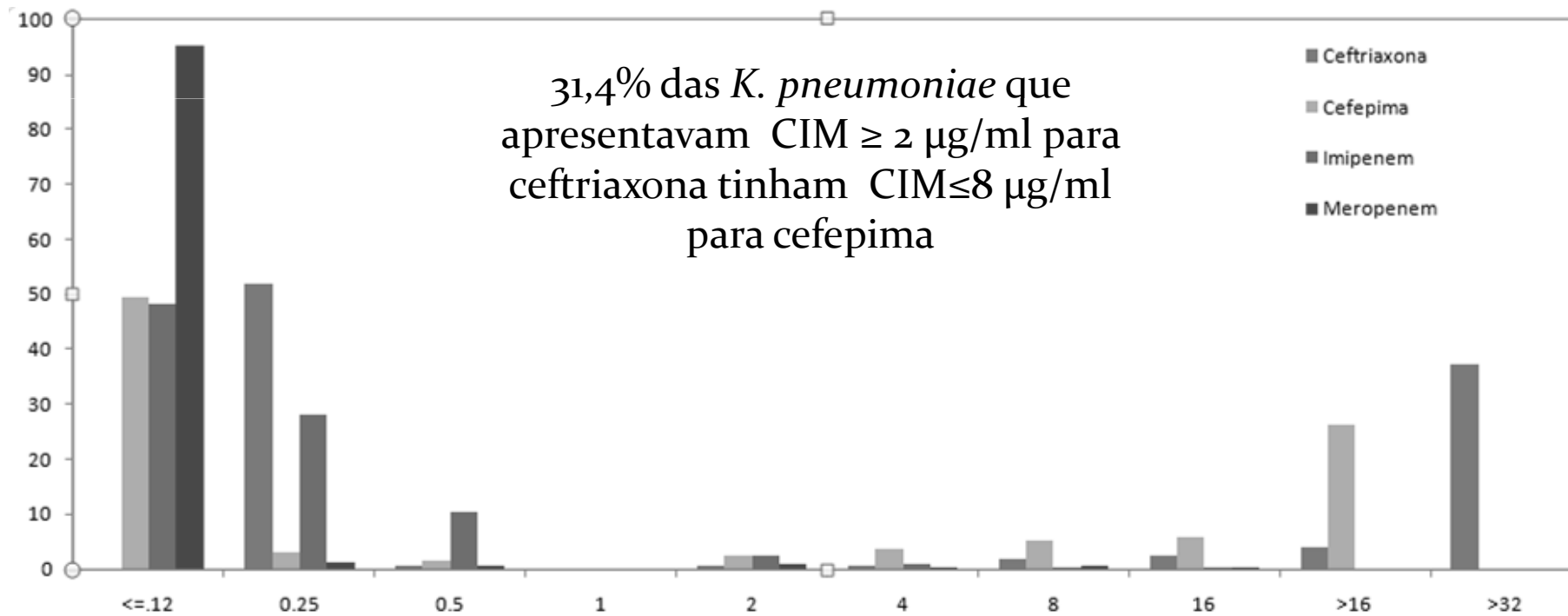


FIG. 5. Cumulative cefepime MIC distribution.

Distribuição das MICs (%) de 1339 *K. pneumoniae* isoladas em hospitais brasileiros Programa SENTRY (1997-2006).



Journal of Infection (2005) 51, 211-217



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Clinical implications of extended spectrum β -lactamase (ESBL) producing *Klebsiella* species and *Escherichia coli* on cefepime effectiveness[☆]

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Table 2 Cefepime outcomes in patients infected with ESBL producing *Klebsiella* species or *E. coli*

Patient no.	Organism	Site	Cefepime dose	MIC ($\mu\text{g/ml}$)	Susceptibility profile ^a	Clinical cure	Microbiological cure
1	<i>Klebsiella pneumoniae</i>	Lungs	1g IV q12h	128	Resistant	Failure	Failure
2	<i>Klebsiella oxytoca</i>	Lungs	1g IV q12h	4	Susceptible	Success	Success
3	<i>Klebsiella pneumoniae</i>	Lungs	1g IV q12h	<0.5	Susceptible	Failure	Failure
4	<i>Escherichia coli</i>	Lungs	1g IV q12h	4	Susceptible	Failure	Failure
5	<i>Klebsiella pneumoniae</i>	Lungs	1g IV q24h	512	Resistant	Failure	Failure
6	<i>Klebsiella oxytoca</i>	Intra-abdominal	1g IV q12h	1	Susceptible	Success	Success
7	<i>Klebsiella oxytoca</i>	Lungs	1g IV q12h	$\geq 16^b$	Resistant	Failure	Failure
8	<i>Escherichia coli</i>	Lungs	1g IV q24h	4	Susceptible	Success	Success
9	<i>Klebsiella pneumoniae</i>	Lungs	1g IV q24h	4	Susceptible	Failure	Failure
10	<i>Escherichia coli</i>	Blood	1g IV q12h	$\geq 16^b$	Resistant	Success	Success

^a Susceptibility according to NCCLS susceptibility breakpoint for cefepime against *Enterobacteriaceae* (≤ 8 mg/l).

^b MICs not conducted, but microbiology lab reported as ≥ 16 mg/l.

Table 4 Risk estimates for the effect of ESBL presence on cefepime outcomes

Variable	Odds ratio (95% confidence interval)
Unsuccessful clinical response	9.7 (1.4-68.8)
Unsuccessful microbiological response	28.5 (2.6-306.6)
All-cause mortality	2.0 (0.396-10.1)
Infection-related mortality	4.7 (0.375-60.1)

Farmacodinâmica dos β -lactâmicos

	%f Time > MIC	
	Bacteriostático	Bactericida*
Penicilinas	35-40	60-70
Cefalosporinas	30	50
Carbapenens	20	40

* Redução > 3 Log na contagem de unidades formadoras de colônias por mL.



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Cefepime pharmacodynamics in patients with extended spectrum β -lactamase (ESBL) and non-ESBL infections[☆]

Su Young Lee, Joseph L. Kuti, David P. Nicolau*

Table 2 Pharmacodynamic indices and microbiological outcome of each patient with infection due to the ESBL pathogens

Subject	Organism	Infection site	MIC ($\mu\text{g/ml}$)	Dosing regimen	fC_{\min}/MIC	$f\text{AUC}/\text{MIC}$	% $fT > \text{MIC}$	Microbiological outcome
1	<i>K. pneumoniae</i>	Lungs	128	2 g q 12 h	0.0193	18.53	0	Persistence
2	<i>K. oxytoca</i>	Lungs	4	1 g q 12 h	1.912	1905	100	Eradication
3	<i>K. pneumoniae</i>	Lungs	0.25	1 g q 12 h	4.304	10959	100	Persistence
4	<i>E. coli</i>	Lungs	4	1 g q 12 h	1.242	1404	100	Persistence
5	<i>K. pneumoniae</i>	Lungs	512	1 g q 24 h	0.0222	13.04	0	Persistence
6	<i>K. oxytoca</i>	Blood	1	1 g q 12 h	18.58	10693	100	Eradication
7	<i>K. oxytoca</i>	Lungs	16	1 g q 12 h	0.0502	205.2	8.3	Persistence
8	<i>E. coli</i>	Lungs	4	1 g q 24 h	2.954	2333	100	Eradication
9	<i>K. pneumoniae</i>	Lungs	4	1 g q 24 h	1.830	1211	100	Persistence
10	<i>E. coli</i>	Blood	16	1 g q 12 h	0.9243	545.9	93.33	Eradication

Table 3 Pharmacodynamic indices and microbiological outcome of each patient with infection due to the non-ESBL pathogens

Subject	Organism	Infection site	MIC ($\mu\text{g/ml}$)	Dosing regimen	fC_{\min}/MIC	$f\text{AUC}/\text{MIC}$	% $fT > \text{MIC}$	Microbiological outcome
1	<i>K. pneumoniae</i>	Lungs	0.064	1 g q 12 h	140.3	91190	100	Eradication
2	<i>K. pneumoniae</i>	Lungs	0.032	1 g q 12 h	10.90	95327	100	Eradication
3	<i>K. oxytoca</i>	Lungs	0.047	1 g q 12 h	216.3	143006	100	Eradication
4	<i>K. oxytoca</i>	Lungs	0.032	1 g q 24 h	285.5	192708	100	Eradication
5	<i>K. pneumoniae</i>	Lungs	0.094	1 g q 12 h	26.86	47112	100	Eradication
6	<i>K. pneumoniae</i>	Lungs	0.047	1 g q 12 h	245.0	163503	100	Eradication
7	<i>K. oxytoca</i>	Lungs	0.047	1 g q 12 h	130.9	110816	100	Eradication
8	<i>K. oxytoca</i>	Lungs	0.047	1 g q 12 h	136.2	134337	100	Eradication

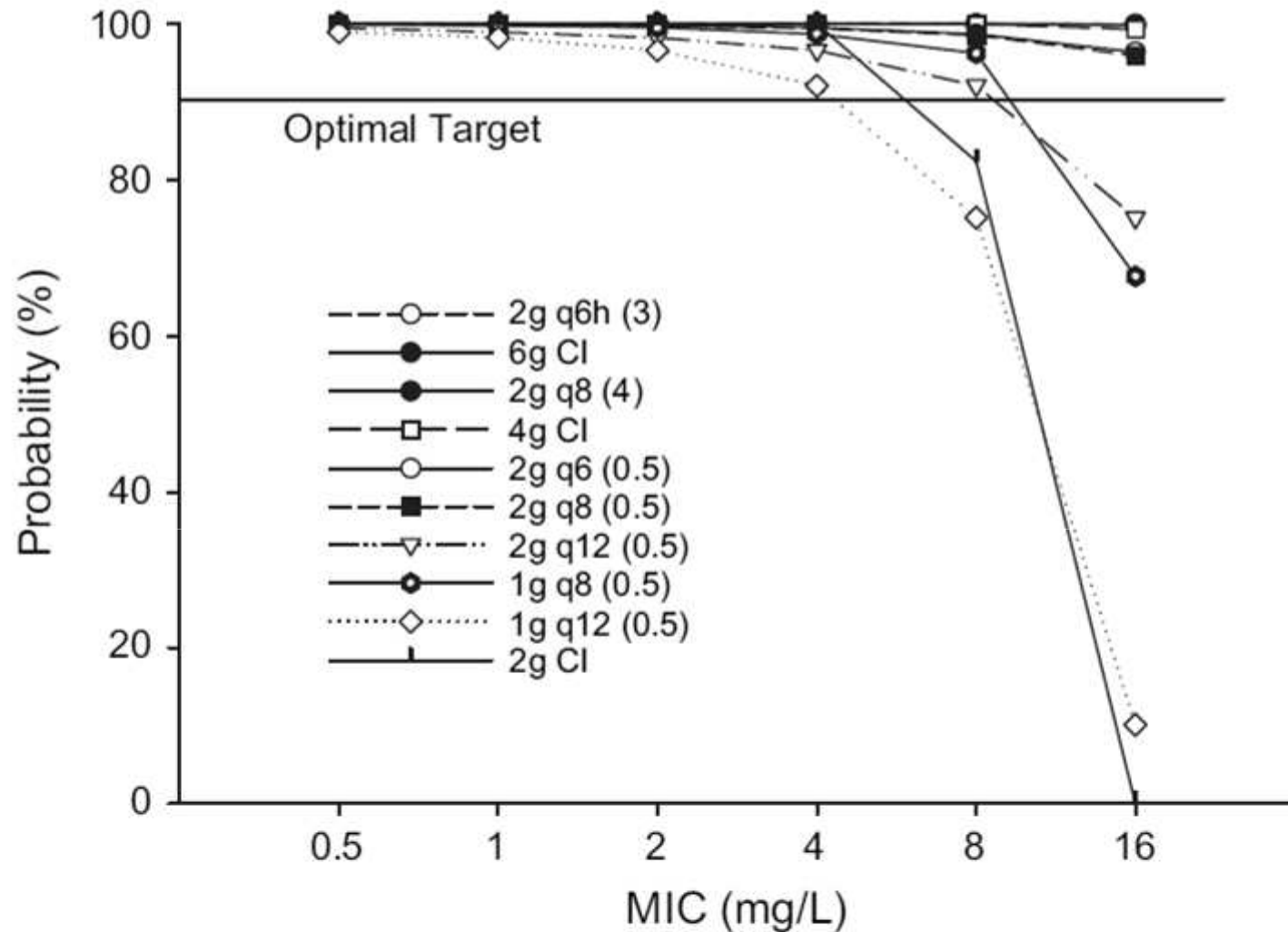


Figure 1 Probability of target attainment (PTA) of each drug regimen (infusion time) to obtain 50% $fT > MIC$ for simulated subjects with CL_{CR} between 60 and 120 ml/min.

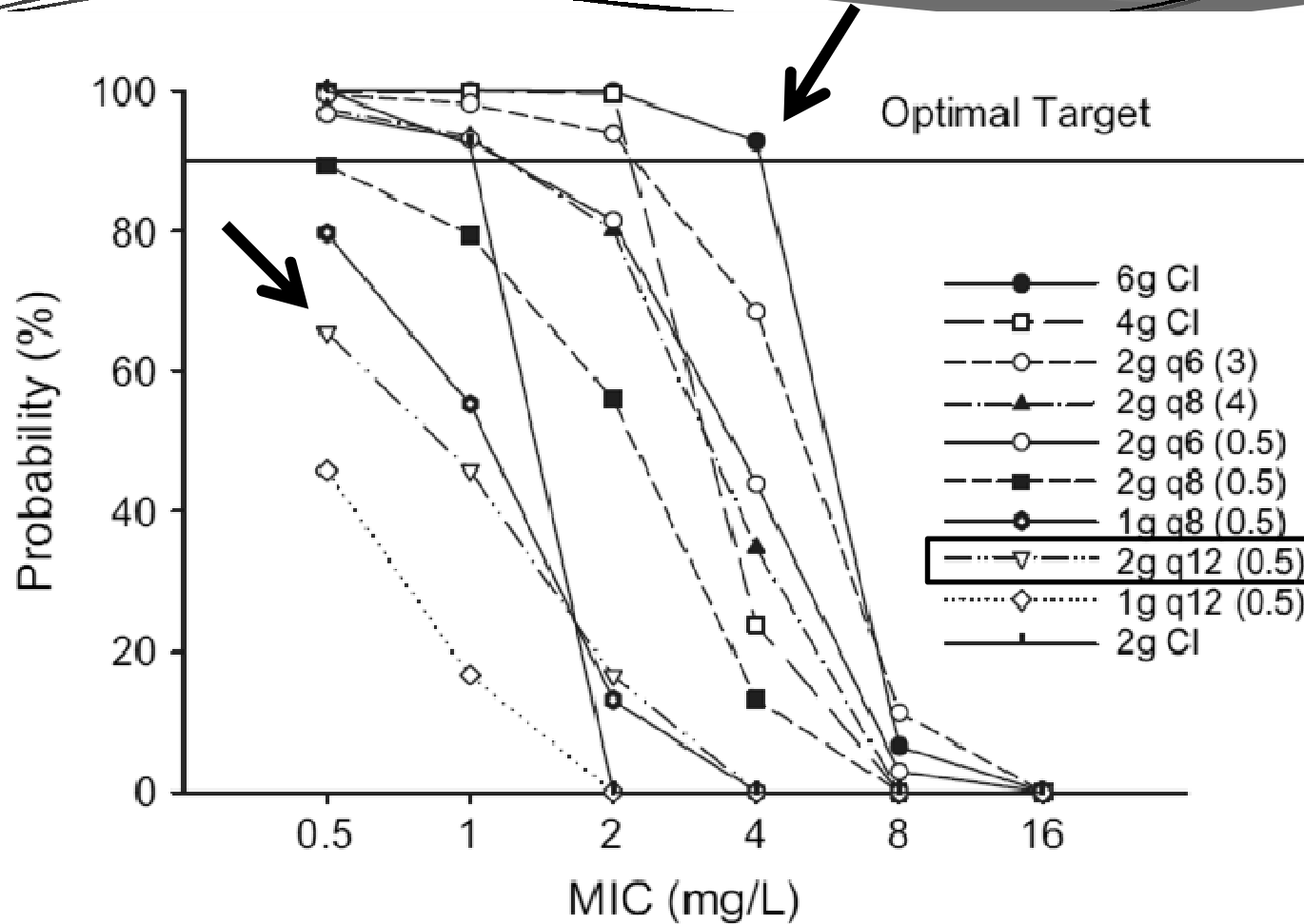


Figure 2 Probability of target attainment (PTA) of each drug regimen (infusion time) to obtain $fC_{min}/MIC > 7.6$ for simulated subjects with CL_{CR} between 60 and 120 ml/min.

Cefepime – Administração Intermitente

J Antimicrob Chemother. 2006 Nov;58(5):987-93.

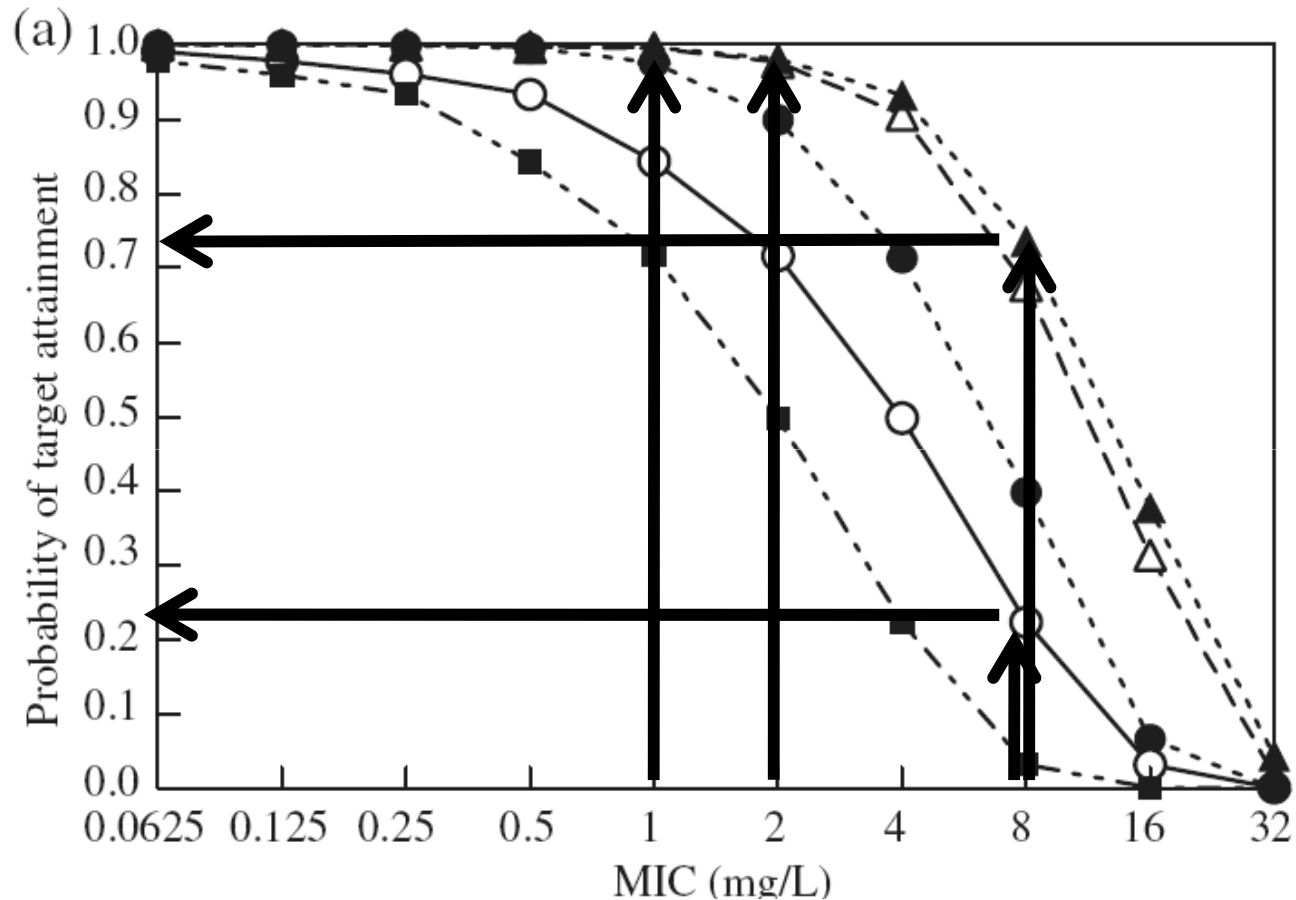


Figure 3. Probability of target attainment for 1000 simulated subjects given cefepime as (a) intermittent administration (2 g every 8 h, filled triangles; 1 g every 4 h, open triangles; 1 g every 6 h, filled circles; 2 g every 12 h, open circles; 1 g every 12 h, filled squares) Roos *et al.*, 2006

Cefepime – Infusão contínua

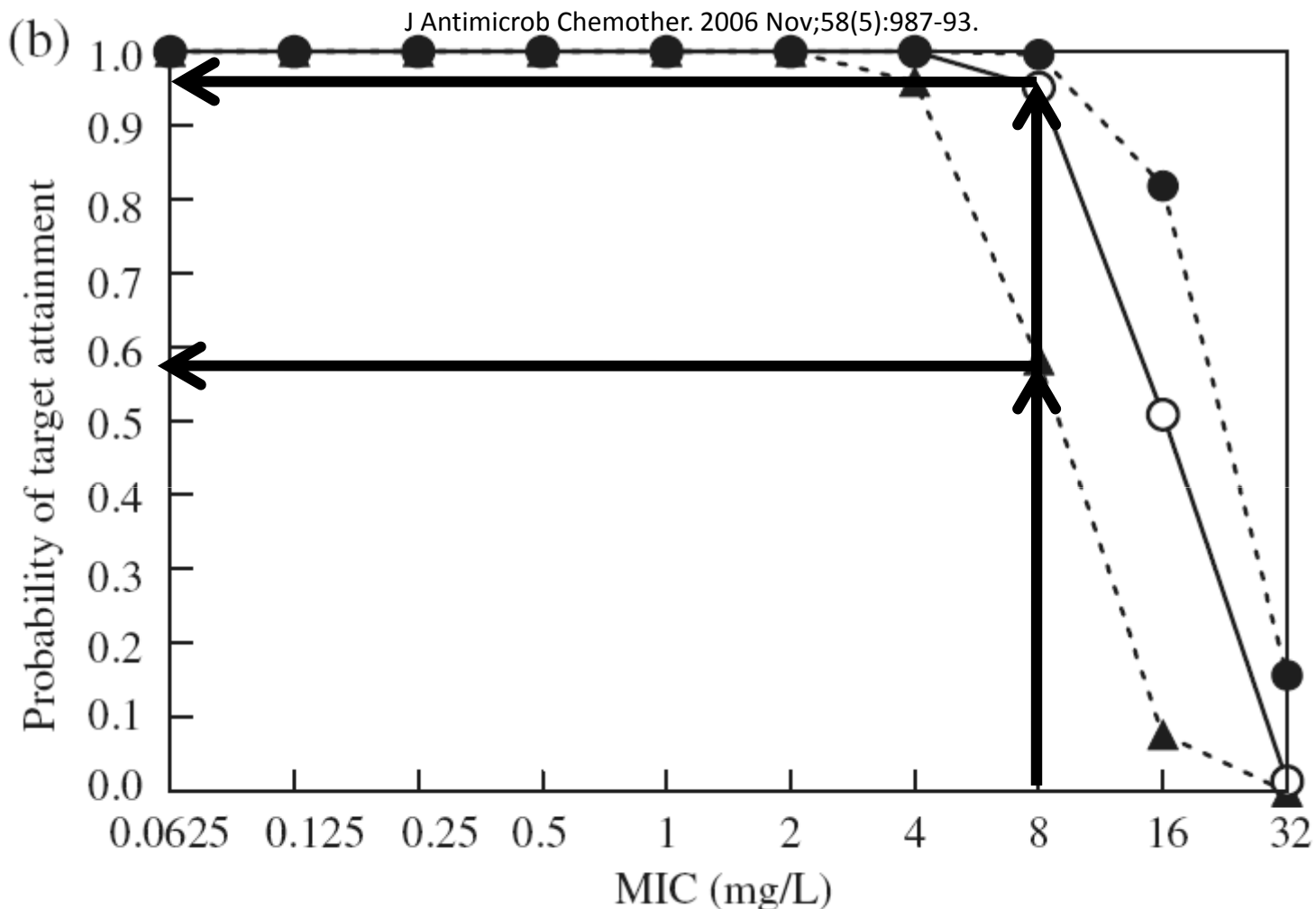


Figure 3. Probability of target attainment for 1000 simulated subjects infusion with a loading dose of 0.5 g (2g/day, filled triangles; 4g/day, open circles; 6g/day, filled circles). The chosen target for the analysis was 65% of the dosing interval of free-cefepime plasma concentrations to be in excess of the MIC.



Sugestão da Sociedade Brasileira de Infectologia

Prescrição de cefepima - Doses habituais

- As enterobactérias devem ser consideradas **sensíveis** à cefepima quando a **CIM for $\leq 1 \mu\text{g/ml}$** , **intermediárias** quando a **CIM for de 2 a $4 \mu\text{g/ml}$** , e **resistentes** quando a **CIM for $\geq 8 \mu\text{g/ml}$** .



Agência Nacional de
Vigilância Sanitária



NOTA TÉCNICA Nº 1/2010

**Medidas para identificação,
prevenção e controle de infecções
relacionadas à assistência à saúde
por microrganismos
multiresistentes**

Unidade de Investigação e Prevenção das
Infecções e dos Eventos Adversos
Gerência Geral de Tecnologia em Serviços de
Saúde

5. DIRETRIZES PARA A AVALIAÇÃO DA SENSIBILIDADE ANTIMICROBIANA E DETECÇÃO DE ENTEROBACTÉRIAS RESISTENTES AOS CARBAPENÊMICOS

Em laboratórios de microbiologia clínica no Brasil, os critérios a serem utilizados como base para interpretação dos testes de sensibilidade para Enterobacteriaceae deverão ser aqueles contidos no documento M100-S20 do *Clinical and Laboratory Standards Institute (CLSI)* publicado em janeiro de 2010, com as seguintes modificações:

Antimicrobiano	Sensível (µg/mL)	Intermediário (µg/mL)	Resistente (µg/mL)	Potência do Disco (µg)	Sensível (mm)	Intermediário (mm)	Resistente (mm)
Cefepima ^a	≤ 1	2 - 4	≥ 8	30	≥ 24	21 - 23	≤ 20
Ceftazidima ^{a,b}	≤ 1	2 - 4	≥ 8	-	-	-	-
Aztreonam ^a	≤ 1	2 - 4	≥ 8	30	27	24 - 26	23
Ertapenem ^a	≤ 0,5	1	≥ 2	10	≥ 25	22 - 24	≤ 21
Imipenem ^c	≤ 1	2	≥ 4	10	≥ 23	20 - 22	≤ 19
Meropenem ^c	≤ 1	2	≥ 4	10	≥ 23	20 - 22	≤ 19
Colistina ou Polimixina B ^a	≤ 2	-	≥ 4	-	-	-	-
Tigeciclina ^a	≤ 1	2	≥ 4	15	≥ 18	15 - 17	≤ 14

- Pontos de corte preconizados pelo *The European Committee on Antimicrobial Susceptibility Testing (EUCAST)*.
- Não há critérios interpretativos para o método Kirby-Bauer, segundo o EUCAST, para discos de ceftazidima com potência de 30 µg.
- Pontos de corte preconizados pelo CLSI.

Nota: Sempre que forem utilizados os critérios interpretativos preconizados nesta tabela, incluir a seguinte nota no resultado: "Para a interpretação dos testes de sensibilidade foram utilizados os critérios preconizados na nota técnica da ANVISA N°. 01/2010".