SOCIEDADE BRASILEIRA DE FARMÁCIA HOSPITALAR
E SERVIÇOS DE SAÚDE

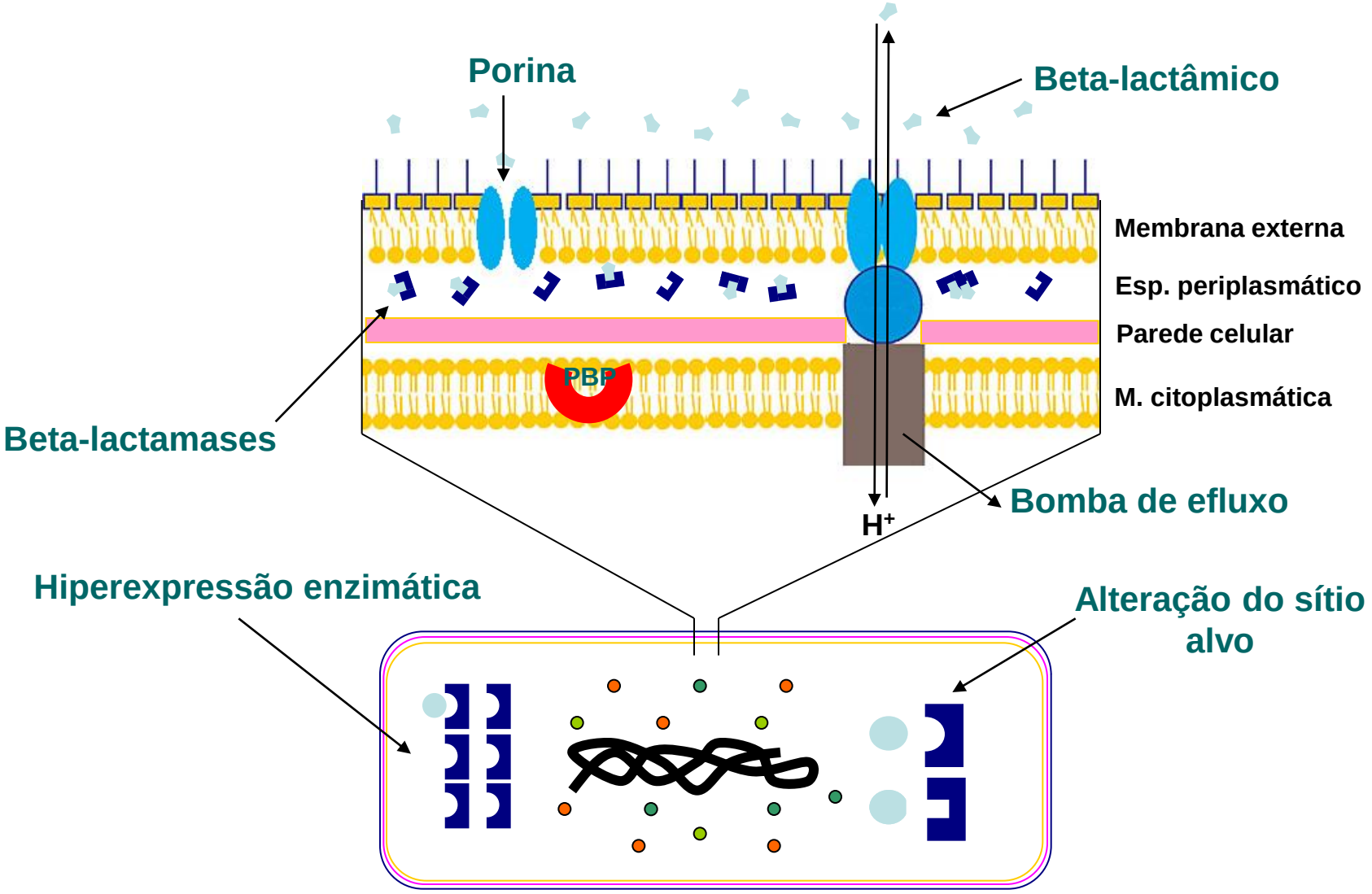
— Farmacêuticos cuidando da saúde e do bem estar das pessoas —

ESTRATÉGIAS PARA O
USO RACIONAL DE
ANTIMICROBIANOS

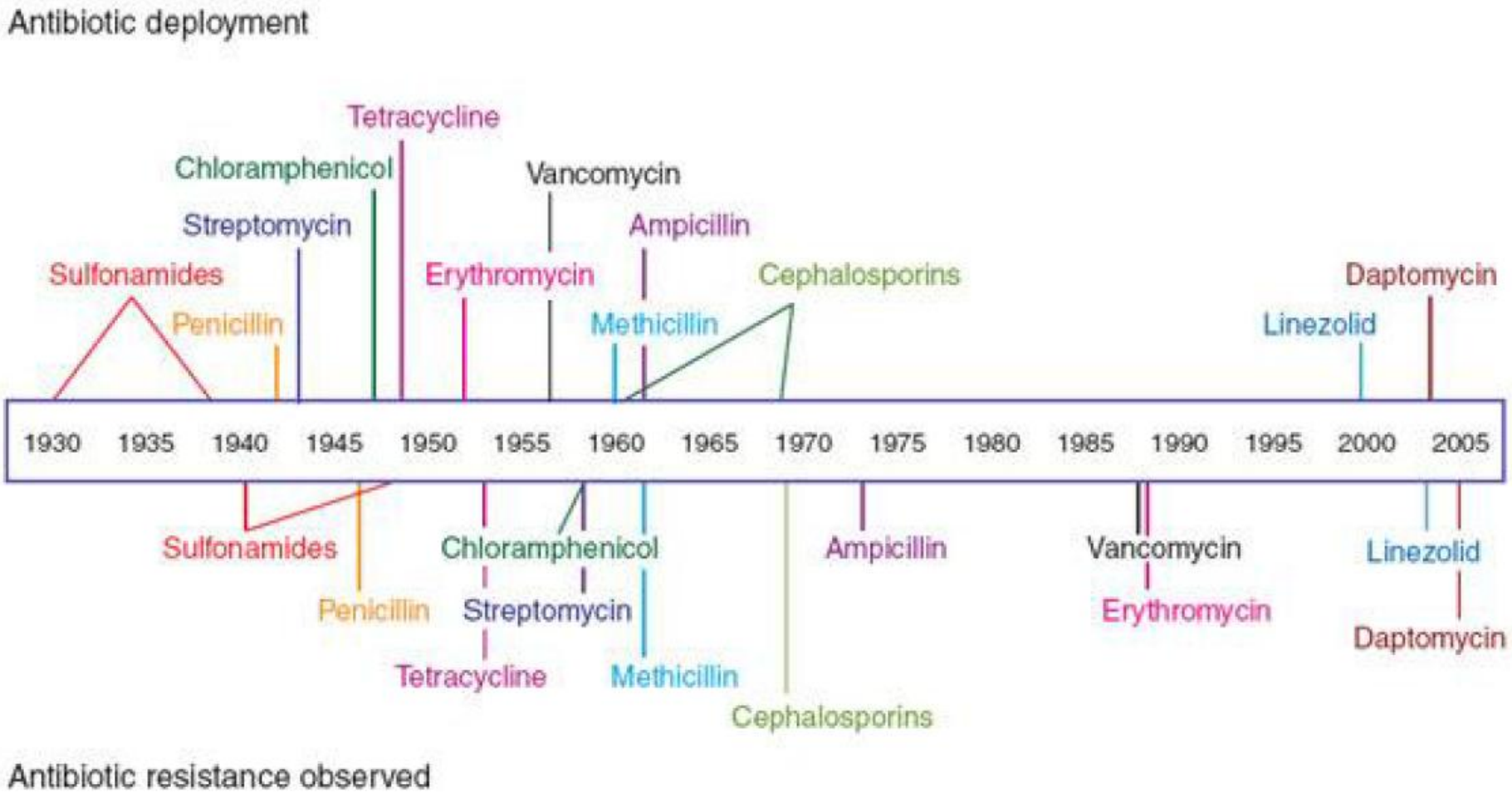
Resistência Microbiana: o que há de novo?

Jussara Kasuko Palmeiro
jussarakp@ig.com.br
Hospital de Clínicas
Universidade Federal do Paraná

Mecanismos de resistência



Linha do tempo da resistência antimicrobiana



O que continua "velho"?

Nosocomial Bloodstream Infections in Brazilian Hospitals: Analysis of 2,563 Cases from a Prospective Nationwide Surveillance Study[▽]

40 %

TABLE 2. Distribution of pathogens most commonly isolated from monomicrobial nBSIs and associated crude mortality rates for all patients in ICUs and patients in non-ICU wards

Pathogen	% BSI (rank)			Crude mortality (%)		
	Total (n = 2,447)	ICU (n = 1,196)	Non-ICU (n = 1,251)	Total (n = 971)	ICU (n = 656)	Non-ICU (n = 315)
S. aureus	15.4 (1)	12.8 (3)[a]	17.9 (1)	31.0	48.2	24.0
CoNS	13.8 (2)	16.6 (1)[a]	11.2 (3)	32.0	46.5	23.2
Klebsiella spp.	13.2 (3)	11.8 (4)[b]	14.5 (2)	34.7	55.2	24.8
Acinetobacter spp.	12.5 (4)	15.2 (2)[a]	10.0 (4)	52.1	65.5	39.6
P. aeruginosa	8.9 (5)	10.0 (5)	7.9 (5)	48.9	61.5	39.0
Enterobacter spp.	6.1 (6)	5.8 (7)	6.4 (6)	30.2	61.4	17.1
Candida spp.	5.6 (7)	7.4 (6)[a]	3.9 (7)	68.6	85.9	53.4
Enterococcus spp.	4.5 (8)	5.5 (8)[b]	3.6 (9)	49.5	64.2	36.2
Serratia spp.	3.5 (9)	3.2 (9)	3.8 (8)	40.0	60.0	29.1
Proteus spp.	1.6 (10)	1.8 (10)	1.6 (10)	44.7	61.1	30.0

[a] $P < 0.001$ for patients in ICU vs. patients in non-ICU wards.
[b] $P < 0.05$ for patients in ICU vs. patients in non-ICU wards.

43,7% de *S. aureus* = MRSA
25% de *Enterococcus* sp. = VRE

> 50% *Klebsiella* sp. = ESBL
> 50% de *Acinetobacter* spp. = R IMI

Marra et al. JCM, May 2011

O que há de novo?

1°lugar: *S. aureus* (MRSA)

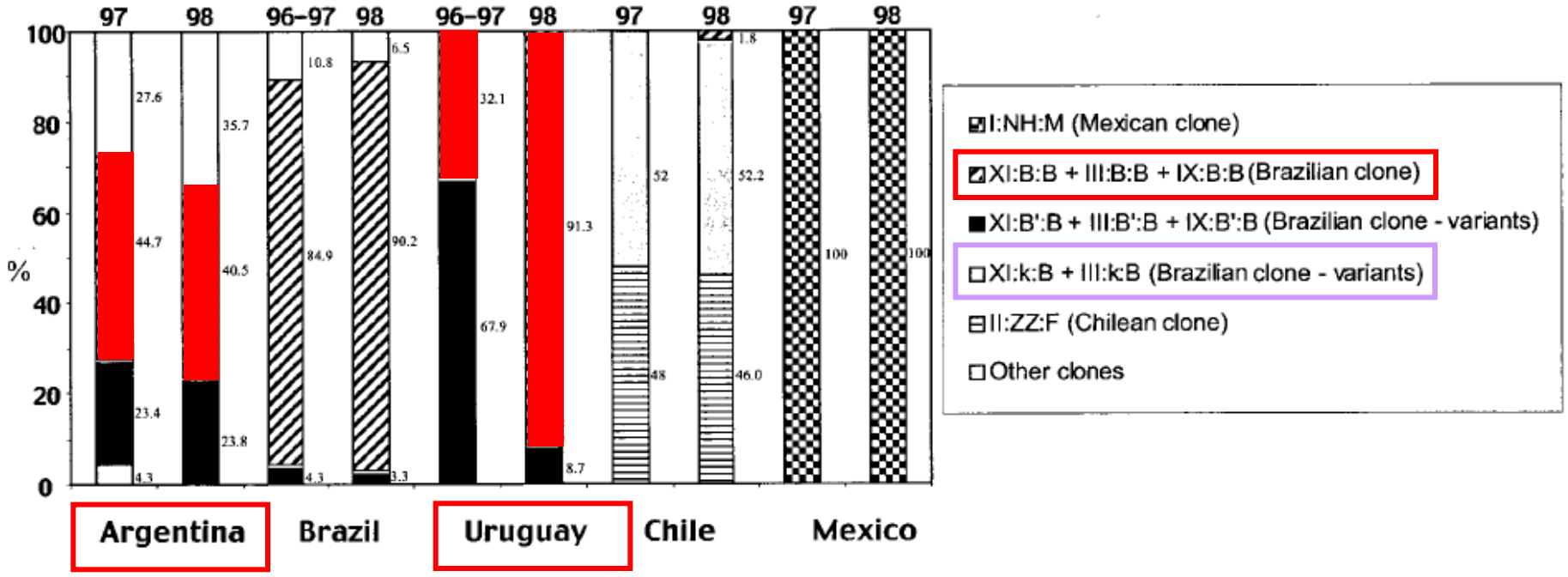
- Nos últimos anos...
  - Aumento de BSI em pacientes hospitalizados
  - Cepas diferentes do clone BR (BEC-MRSA)
    - S aos atbs não-beta-lactâmicos (SUT)
    - SCC*mec* IV

ORIGEM COMUNITÁRIA

CLSI, 2013

Disseminação de diferentes clones

Three-Year Assessment of Methicillin-Resistant *Staphylococcus aureus* Clones in Latin America from 1996 to 1998

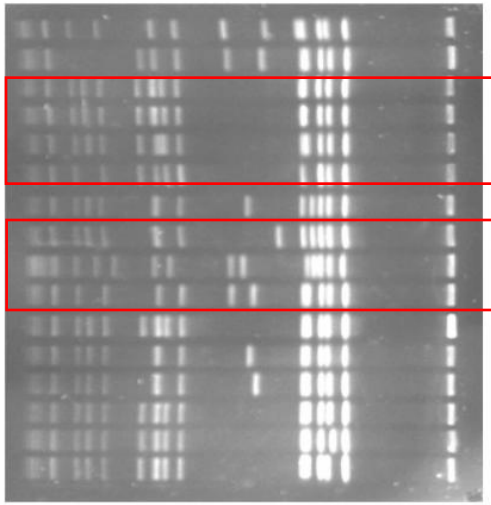


Aires de Sousa et al. JCM, June 2001

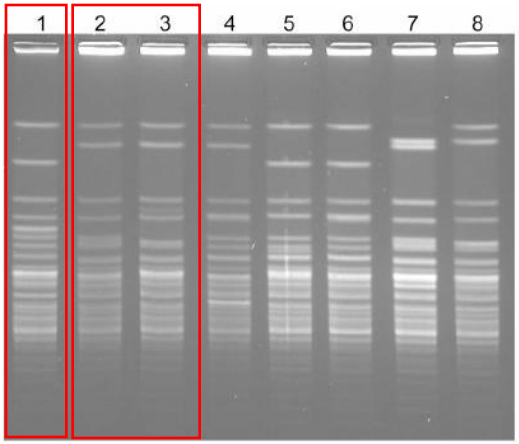
Disseminação de diferentes clones

Methicillin-Resistant *Staphylococcus aureus* USA300 and Vancomycin-Resistant *Enterococcus faecalis*: A United States-Colombian Microbial Connection?

MRSA



Isolate	City or State of Origin	Toxin Profile and *arcA* gene[c]	ST	SCC*mec* IV subtype
Col-131	Villavicencio	*bsaA, seq, sek*	923[d]	a
Col-177	Bogotá, DC	*bsaA seq, sek*	8	Non a,b,c
HUV-01	Cali	*bsaA, seq, sek*	8	Non a,b,c
HUV-03	Cali	*bsaA, seq, sek*	ND	Non a,b,c
HUV-07	Cali	*bsaA, seq, sek*	8	Non a,b,c
HUV-05	Cali	*bsaA, seq, sek*	8	Non a,b,c
USA300[a]	Texas	*bsaA, seq, sek, arcA*	8	a
USA400	North Dakota	ND	1	a
USA300[b]	Nebraska	*bsaA, seq, sek*	8	b
CA-12	Cartagena	*bsaA*	8	Non a,b,c
CA-14	Cartagena	*bsaA*	ND	Non a,b,c
CA-15	Cartagena	*bsaA, seq, seK*	8	a
CA-16	Cartagena	*bsaA, seq, seK*	ND	Non a,b,c
CA-17	Cartagena	*bsaA*	ND	Non a,b,c
CA-18	Cartagena	*bsaA*	ND	Non a,b,c

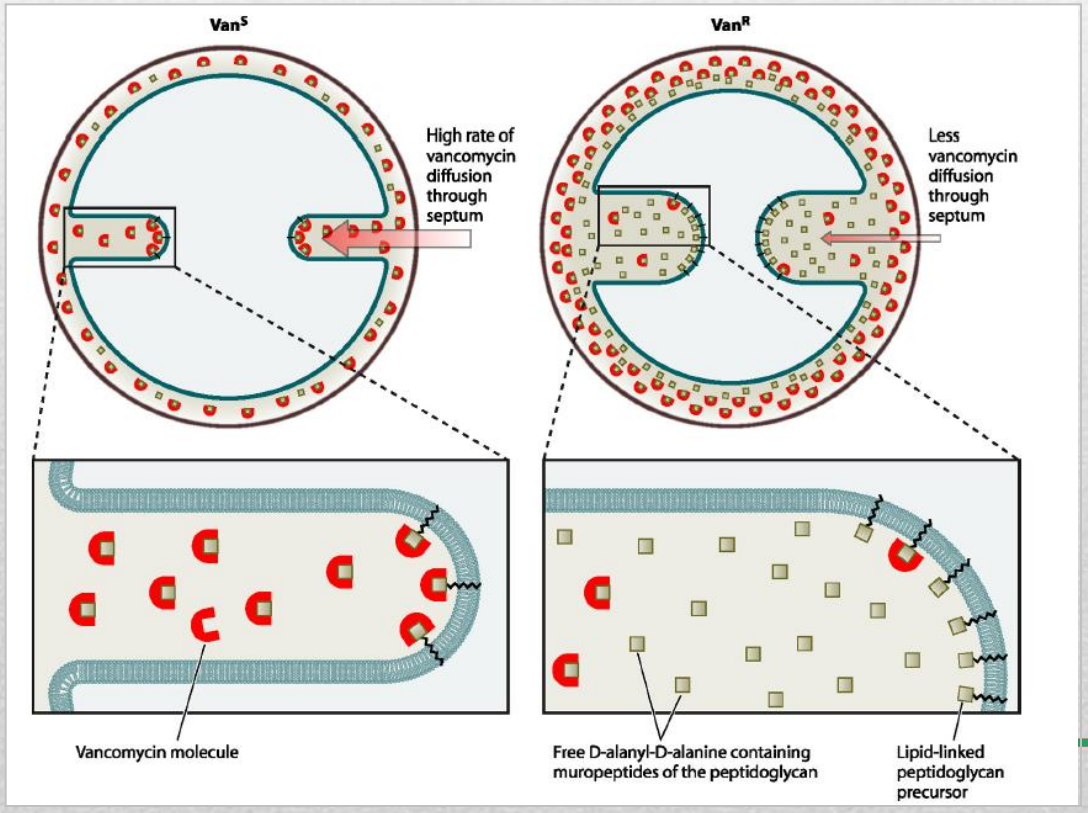


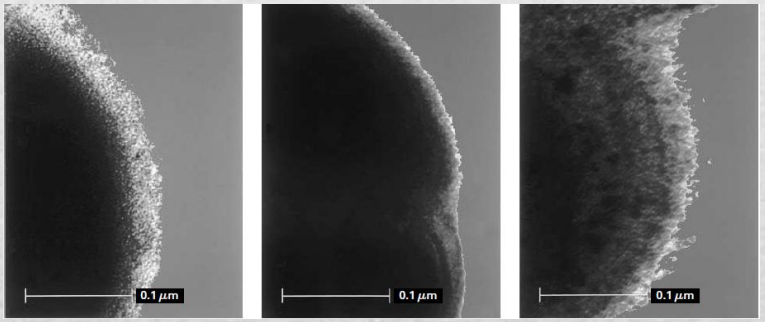
VRE

Arias et al. N Engl J Med, November 2009

S. aureus (VISA)

- 1° caso – Japão, 1997
- *S. aureus* VAN CIM 4 a 8 ug/mL



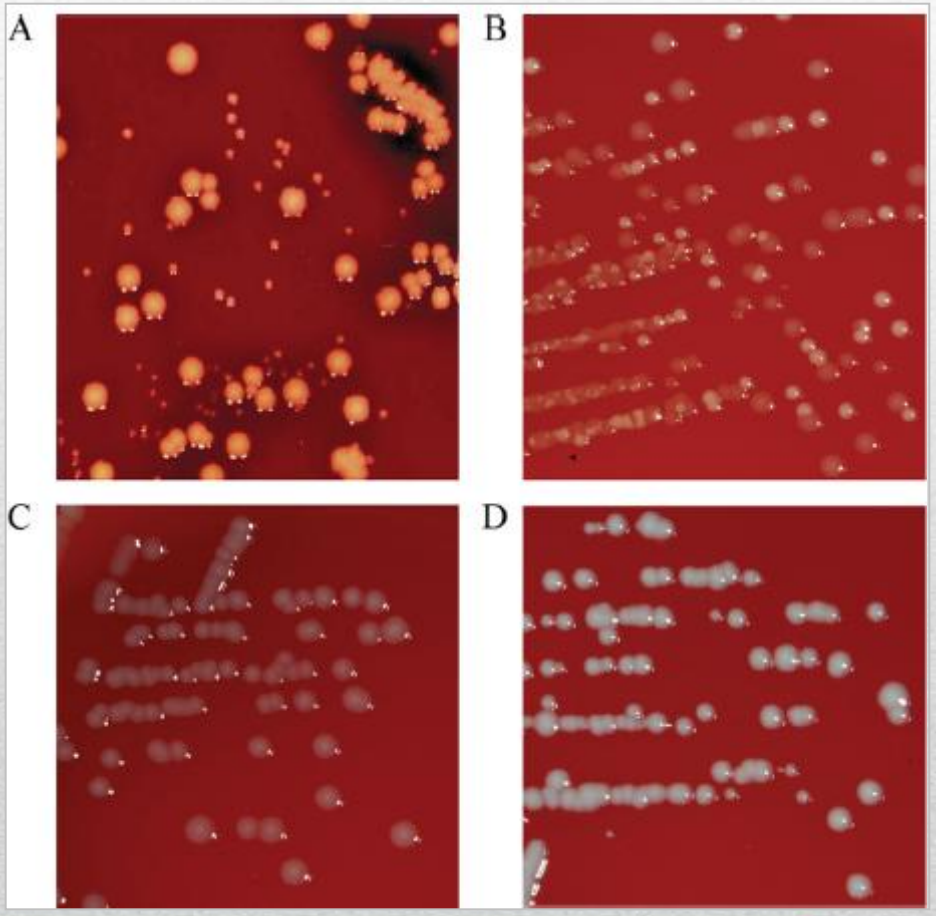


Howden et al. CMR, January 2010

S. aureus (VISA)

- Aumento de falha terapêutica ----- aumento da mortalidade
  - VISA x hVISA

Dificuldade em detectar!!!



A. SC = VISA e LC = VSSA
B. YC = VISA e GC = VSSA
C. GC = VSSA
D. WC = VISA

Howden et al. CMR, January 2010

Como detectar?

Reduced Vancomycin Susceptibility in *Staphylococcus aureus*, Including Vancomycin-Intermediate and Heterogeneous Vancomycin-Intermediate Strains: Resistance Mechanisms, Laboratory Detection, and Clinical Implications

TABLE 5. Laboratory detection of hVISA and accuracy of methods compared to those of modified population analysis/area under the curve[a]

Method	Sensitivity	Specificity	Reference(s)
Vancomycin broth MIC[b]	11%	100%	372
BHIA + vancomycin at 6 μg per ml, 10 μl of a 0.5-McFarland-standard suspension (BHIA6V)[c]	48 h, 4.5–12%	48 h, 68–100%	370, 389, 393
MHA + teicoplanin at 5 μg per ml, 10 μl of a 2-McFarland-standard suspension (MHA5T)[d]	48 h, 65–79%	48 h, 35–95%	82, 252, 370, 389, 393
MHA + teicoplanin at 5 μg per ml, 10 μl of a 2-McFarland-standard suspension[e]	48 h, 98%	48 h, 53%	82
MHA + vancomycin at 5 μg per ml, 10 μl of a 0.5-McFarland-standard suspension	48 h, 1–20%	48 h, 59–99%	370, 372
Simplified PAP[f]	48 h, 71%	48 h, 88%	372
Macromethod Etest (MET)	48 h, 69–98.5%	48 h, 89–94%	174, 289, 370, 372, 389
Etest GRD	24 h, 70–77%	24 h, 98–100%	174, 393
	48 h, 93–94%	48 h, 82–95%	

[a] In all studies, vancomycin population analysis/area under the curve (PAP/AUC) was considered the "gold standard" for calculating sensitivity and specificity.
[b] Evaluation of vancomycin broth MICs included detection of VISA and hVISA. By definition, hVISA will not be detected by determinations of broth MIC.
[c] BHIA6V is the screening plate recommended by the CDC and the Clinical and Laboratory Standards Institute for the detection of VRSA and VISA strains with vancomycin MICs of ≥8 μg per ml (http://www.cdc.gov) (53), which is spot inoculated with 10 μl from a 0.5-McFarland-standard suspension and read at 24 and 48 h. The culture is considered positive if there is growth of 2 or more colonies.
[d] MHA5T is the screening plate recommended by the Comité de l'Antibiogramme de la Société Française de Microbiologie (http://www.sfm.asso.fr),which is spot inoculated with 10 μl from a 2-McFarland-standard suspension and read at 24 and 48 h. The culture is considered positive if there is growth of 1 or more colonies.
[e] This analysis included some isolates with a hetero-teicoplanin-resistant but vancomycin-susceptible phenotype by population analysis.
[f] Simplified PAP consists of inoculating BHIA with 4 μg per ml of vancomycin with 10 μl from a 0.5-McFarland-standard suspension and reading at 24 and 48 h for any growth.

Howden et al. CMR, January 2010

Opções terapêuticas

Daptomicina – só ou em combinações

- Melhor combinação – com OXA (testando CFO)

Linezolida

- Para pneumonia – apresenta menores taxas de toxicidade que VAN

Tigeciclina – bacteriostática

Ceftaroline – novo beta-lactâmico para tratar MRSA

- Aprovado só para infecções em tecidos moles e pneumonia comunitária.
- Incluído no CLSI 2013

CLSI, 2013

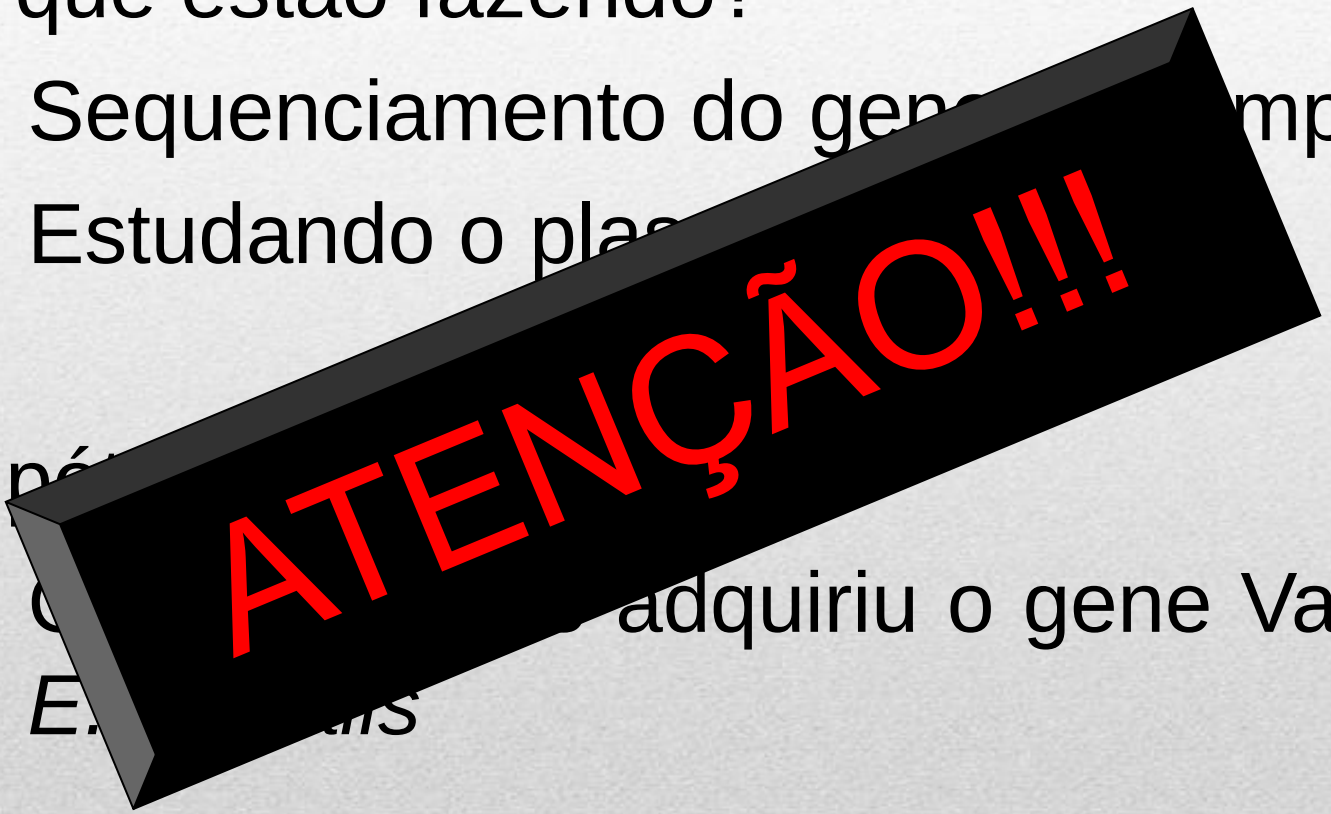
1° VRSA no Brasil

- HC/SP
- Isolado de bacteremia
- Características da cepa:
  - R a VAN (CIM = 256 µg/mL); S a TEICO
  - gene VanA – plasmídio pBRZ01
  - Diferente das cepas dos EUA
  - Semelhante as cepas comunitárias da Austrália (SCC*mec* IVa)

CLSI, 2013

1° VRSA no Brasil

- O que estão fazendo?
  - Sequenciamento do gen[illegible]mpleto
  - Estudando o pla[illegible]
- Hip[illegible]
  - C[illegible] adquiriu o gene VanA de *E.[illegible]ns*



CLSI, 2013

2° lugar: *Enterobacteriaceae*

1° relato de SHV-2 SMA e KPN na Alemanha

Detecção ESBL (CLSI)

Detecção de ESBL somente para fins epidemiológicos

1983

1999

2001

2010

2012/2013...

Relato de fracasso terapêutico e óbitos

Carbapenemases em enterobactérias

Triagem de carbapenamases (CLSI)

TÚNEL DO TEMPO

Beta-lactamases

- ESBLs
  - Descritas - várias enterobactérias
    - TEM (204)
    - SHV (168)
    - CTX-M (134) – 1, 2, 8, 9 e 25
      (Emergence of CTX-M15)
    - GES (22)
    - PER (7)
    - VEB (9)

http://www.lahey.org/studies/webt.htm

Carbapenemases em Enterobactérias: O que temos até agora?

Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: an Evolving Crisis of Global Dimensions

TABLE 1 Types, classification, variants, and species distribution of plasmid-mediated carbapenemases encountered in *Enterobacteriaceae*

Type	Molecular class (subclass)[a]	Functional group[b]	Variants	Species
KPC	A	2f	KPC-2 to -13	*K. pneumoniae, E. coli, Klebsiella oxytoca, S. marcescens, Enterobacter* spp., *C. freundii, Salmonella enterica, Raultella* spp.
VIM	B (B1)	3a	VIM-1, -2, -4, -5, -6 VIM-11, -12, -13, -19, -23 VIM-24, -25, -26, -27, -32	*K. pneumoniae, E. coli, K. oxytoca, S. marcescens* *Serratia liquefaciens, Enterobacter* spp., *C. freundii* *Morganella morganii, Proteus stuartii, P. mirabilis*
IMP	B (B1)	3a	IMP-1, -3, -4, -6, -8	*K. pneumoniae, E. coli, K. oxytoca, S. marcescens*

Acinetobacter sp.: OXA-23, OXA-24/40, OXA-58 (‘fracas’)
OXA-48 – KPN: atividade hidrolítica 10x >

SPM, GIM, SIM, AIM, DIM, KHM e FIM

Tzouvelekis et al. CMR, October 2012

Já temos NDM no Brasil

Agência Nacional de Vigilância Sanitária

COMUNICAÇÃO DE RISCO Nº 001/2013 - GVIMS/GGTES-ANVISA

Circulação de micro-organismos com mecanismo de resistência denominado "*New Delhi Metalobetalactamase*" ou NDM no Brasil.

- Março, 2013. Dois pacientes (I e C) no RS. *Providencia rettgeri* e *Enterobacter cloacae*

Global spread of antibiotic resistance: the example of New Delhi metallo-β-lactamase (NDM)-mediated carbapenem resistance

Enterobacteriaceae, *A. baumannii* e *P. aeruginosa*

Johnson A P and Woodford N. JMM, 2013

Desafios na detecção laboratorial

TABLE 2 Hydrolytic efficiencies of representative carbapenemase variants against various β-lactam substrates

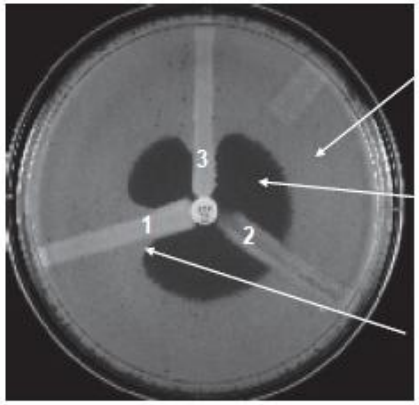
β-Lactamase	Hydrolytic efficiency (k_{cat}/K_m) (s^{-1} μM^{-1})[a] against:								Reference
	Imipenem	Meropenem	Ceftazidime	Cefotaxime	Aztreonam	Cefoxitin	Cephalothin	Penicillin G	
KPC-2	0.29	0.27	ND	0.10	0.08	0.002	0.84	1.90	271
KPC-3	1.90	1.40	0.03	0.50	ND	0.50	3.50	ND	4
VIM-1	0.13	0.26	0.08	0.68	—	0.20	5.10	0.04	93
VIM-2	3.80	2.50	0.05	5.80	—	1.20	11.8	4.0	74
VIM-4	23.0	0.90	ND	ND	—	ND	36.0	3.10	137
VIM-5	0.29	0.05	0.001	0.09	—	ND	ND	0.26	95
VIM-19	6.0	2.0	0.02	30.0	—	0.50	ND	5.0	227
VIM-27	0.26	ND	ND	0.82	—	0.03	8.30	ND	198
IMP-1	1.20	0.12	0.18	0.35	—	2.0	2.40	0.62	136
IMP-4	0.35	0.18	0.07	0.14	—	ND	0.43	0.08	51
NDM-1	0.21	0.25	0.03	0.58	—	0.02	0.40	0.68	273
NDM-4	0.46	0.31	0.06	1.20	—	—	0.50	ND	189
OXA-48	0.14	<0.001	0.001	0.05	—	ND	0.15	6.10	217

[a] ND, not determined; —, no hydrolysis detected.

Tzouvelekis et al. CMR, October 2012

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Cloverleaf test (modified Hodge test) for detecting carbapenemase production in *Klebsiella pneumoniae*: be aware of false positive results



E. coli ATCC® 25922

Inhibition of *E. coli* ATCC® 25922 by ertapenem

Enhanced growth of *E. coli* ATCC® 25922. Carbapenemase produced by *K. pneumoniae* ATCC® BAA-1705 inactivated ertapenem that diffused into the media. Thus, there is no longer sufficient ertapenem here to inhibit *E. coli* ATCC® 25922 and an indentation of the zone is noted.

Figure 1. The MHT Performed on a Small MHA Plate.
(1) *K. pneumoniae* ATCC® BAA-1705, positive result;
(2) *K. pneumoniae* ATCC® BAA-1706, negative result;
and (3) a clinical isolate, positive result.

CLSI, 2013

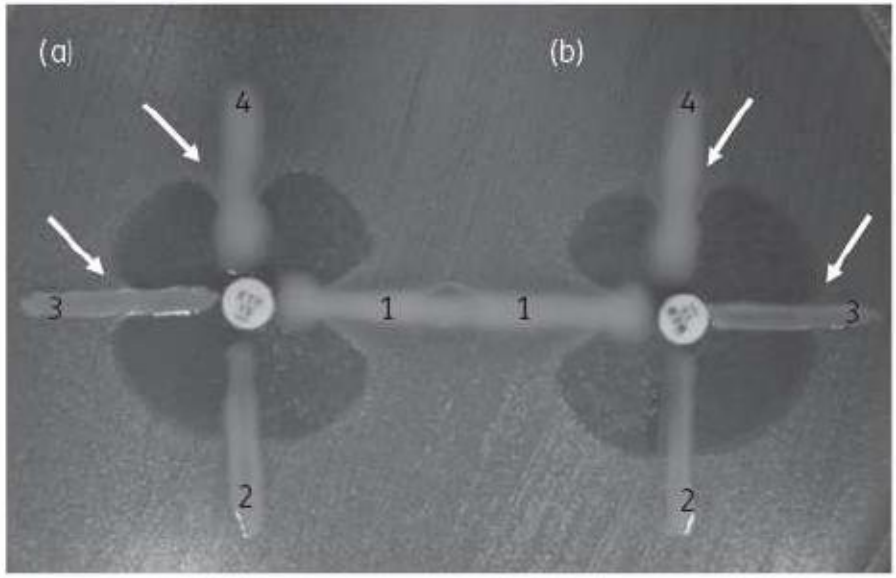


Figure 1. Phenotypic carbapenemase detection by MHT applying the inoculum recommended by CLSI for ertapenem (a) and meropenem discs (b). 1, *K. pneumoniae* ATCC BAA-1705, positive result; 2, *K. pneumoniae* ATCC BAA-1706, negative result; 3, CTX-M-producing *K. pneumoniae* clinical isolate; 4, KPC-producing *K. pneumoniae* clinical isolate. Arrows indicate the similar size of *E. coli* ATCC 25922 grown within the carbapenem disc inhibition zones when testing both carbapenemase producer and carbapenemase non-producer isolates.

Carvalhaes CG et al. JAC, 2010

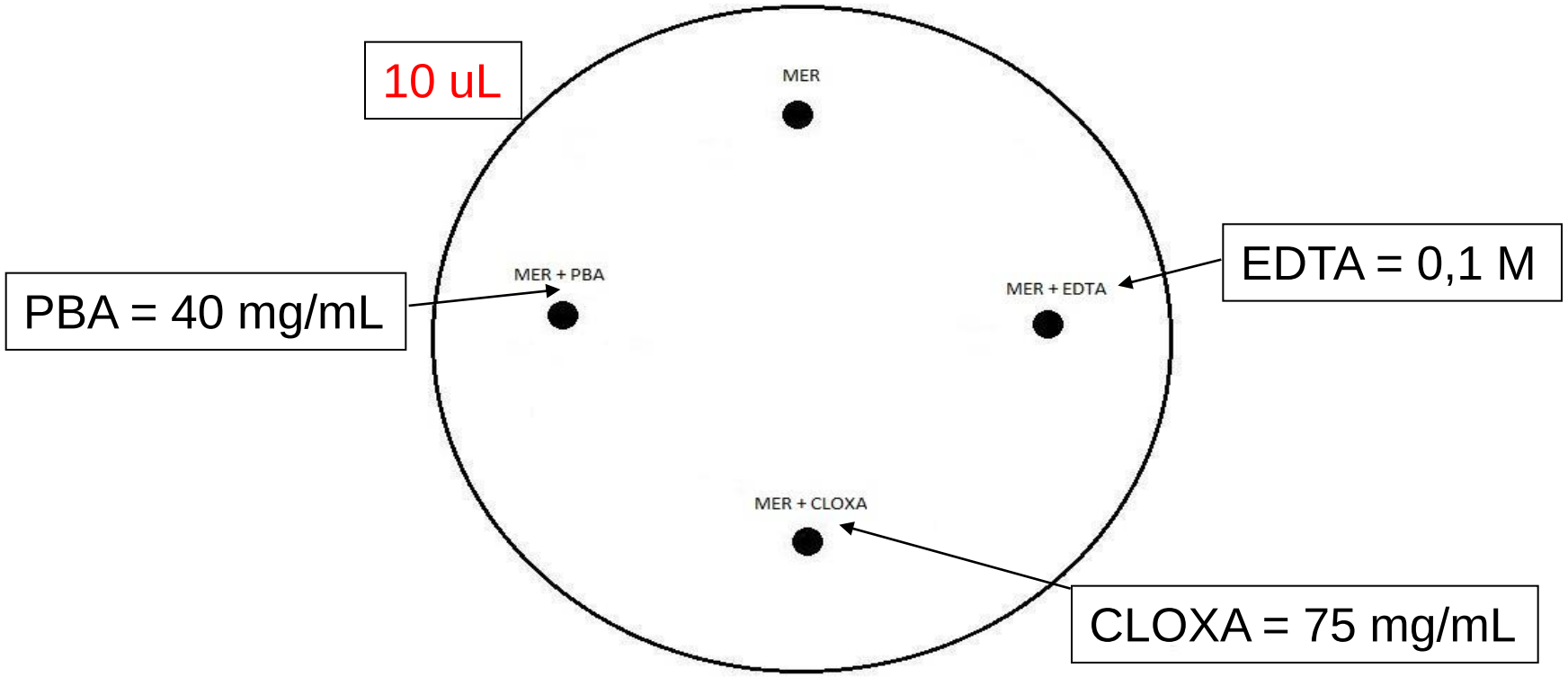
Agência Nacional de
Vigilância Sanitária

NOTA TÉCNICA Nº 01/2013

MEDIDAS DE PREVENÇÃO E CONTROLE DE INFECÇÕES POR ENTEROBACTÉRIAS MULTIRESISTENTES.

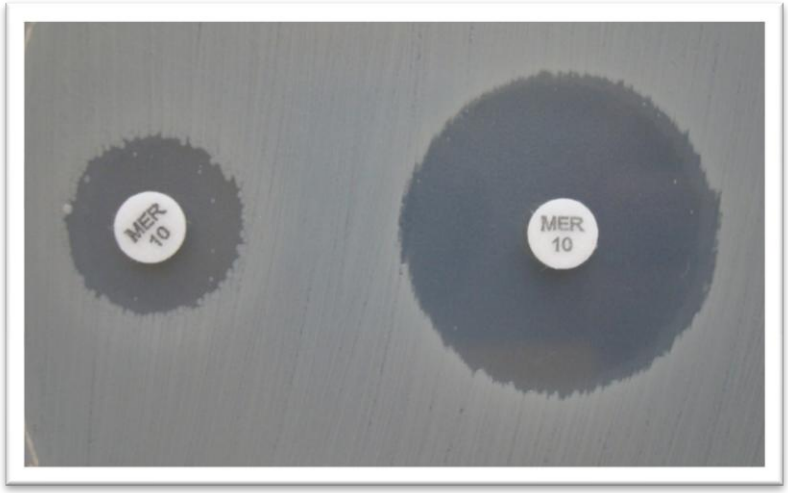
Triagem de CPE

K. pneumoniae/ E. coli			Grupo CESP		
ERT	MER	IMI	ERT	MER	IMI
24 mm; 1 ug/mL	22 mm; 2 ug/mL	22 mm; 2 ug/mL	X	22 mm; 2 ug/mL	22 mm; 2 ug/mL



Interpretação

– MER + EDTA: aumento ≥ 5 mm
– MER + PBA: aumento ≥ 5 mm
– MER + Cloxa: aumento ≥ 5 mm

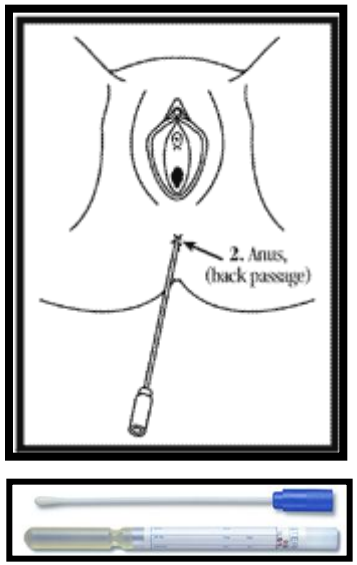


E. cloacae VIM-1

Somente para PBA	Somente para EDTA	PBA e CLOXA
KPC	MBL	AmpC

Lembrar: testes fenotípicos = triagem
Testes moleculares = confirmatórios

Vigilância de CPE



Swab

TSB + ERT

18 h 37ºC

MC

24 h 37ºC

Avaliação das diferentes colônias com crescimento ≤ 27 mm ERT

Opções terapêuticas

- Meta-análise de 34 estudos clínicos para verificar a eficácia de diferentes antibióticos
  - Total de 301 pacientes: 161 com KPC e 140 com MβL
  - Avaliaram a falha terapêutica observada em diferentes regimes de tratamento

Tzouvelekis et al. CMR, October 2012

Tratou e ...

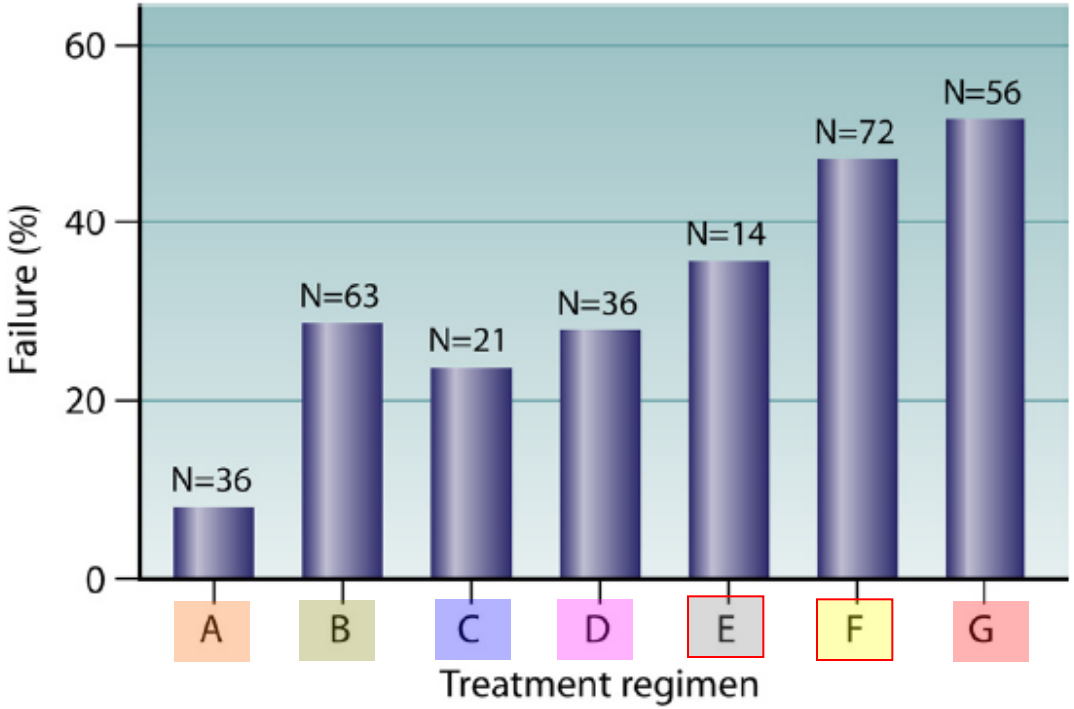


FIG 2 Outcomes of infections caused by carbapenemase-producing *Klebsiella pneumoniae*, according to treatment regimen. Regimen A, combination therapy with ≥2 active drugs, one of which was a carbapenem; regimen B, combination therapy with ≥2 active drugs, not including a carbapenem; regimen C, monotherapy with an aminoglycoside; regimen D, monotherapy with a carbapenem; regimen E, monotherapy with tigecycline; regimen F, monotherapy with colistin; regimen G, inappropriate therapy. Regimen A was superior to regimens B, E, F, and G (for A versus B, E, F, and G, the *P* value was 0.02, 0.03, <0.0001, and <0.0001, respectively). Regimens B, C, and D were superior to regimen G (for B versus G, $P = 0.014$; for C versus G, $P = 0.04$; and for D versus G, $P = 0.03$).

Tzouvelekis et al. CMR, October 2012

Efeito da MIC em CPE

TABLE 5 Results of carbapenem monotherapy in 50 CPE-infected patients from 15 studies[a]

MIC of carbapenem (μg/ml)	No. of patients	No. of successes	No. of failures	% Failure
≤1	17	12	5	29.4
2	12	9	3	25.0
4	7	5	2	28.6
8	6	4	2	33.3
Subtotal	42	30	12	28.6[b]
>8	8	2	6	75.0[b]
Total	50	32	18	36

[a] See references 25, 64, 67, 81, 113, 143, 153, 159, 162, 240, 252, 257, 258, 269, and 275.
[b] $P = 0.02$, odds ratio = 7.5, and 95% confidence interval = 1.32 to 42.52.

Tzouvelekis et al. CMR, October 2012

Mas e aí? Alguma alternativa?

TABLE 7 Experimental antimicrobial agents active against carbapenemase-producing *Enterobacteriaceae*

Drug	Compound type	Relevant target	Reference
BAL30072	Siderophore-containing sulfactam	*Enterobacteriaceae*, including MβL producers	194
Plazomicin (ACHN-490)	Sisomicin derivative	Gram-negative organisms, including carbapenemase producers	149
GSK2251052	Leucyl-tRNA synthetase inhibitor	Gram-negative organisms, including carbapenemase producers	5

TABLE 8 Experimental β-lactamase inhibitors active against carbapenemases from *Enterobacteriaceae*

Inhibitor	Compound type	Inhibition spectrum (β-lactamase classes)	Susceptible carbapenemases[a]	Reference(s)
BLI-489	Penem	A, C, D	KPC type	209
J-110,411 and J-111,225	1-β-Methyl carbapenem	A, C, B	IMP type	183, 184
Mercaptomethyl sulfones	C-6-substituted penicillin sulfone	B	VIM and IMP types	38
2,3-(*S*,*S*)-Disubstituted succinic acids	Succinic acid	B	IMP type	170
Thiomandelic acids	Thiol	B	VIM and IMP types	147, 268
Avibactam (NLX104)	Diazabicyclo-octanone	A, C, D	KPC type	22

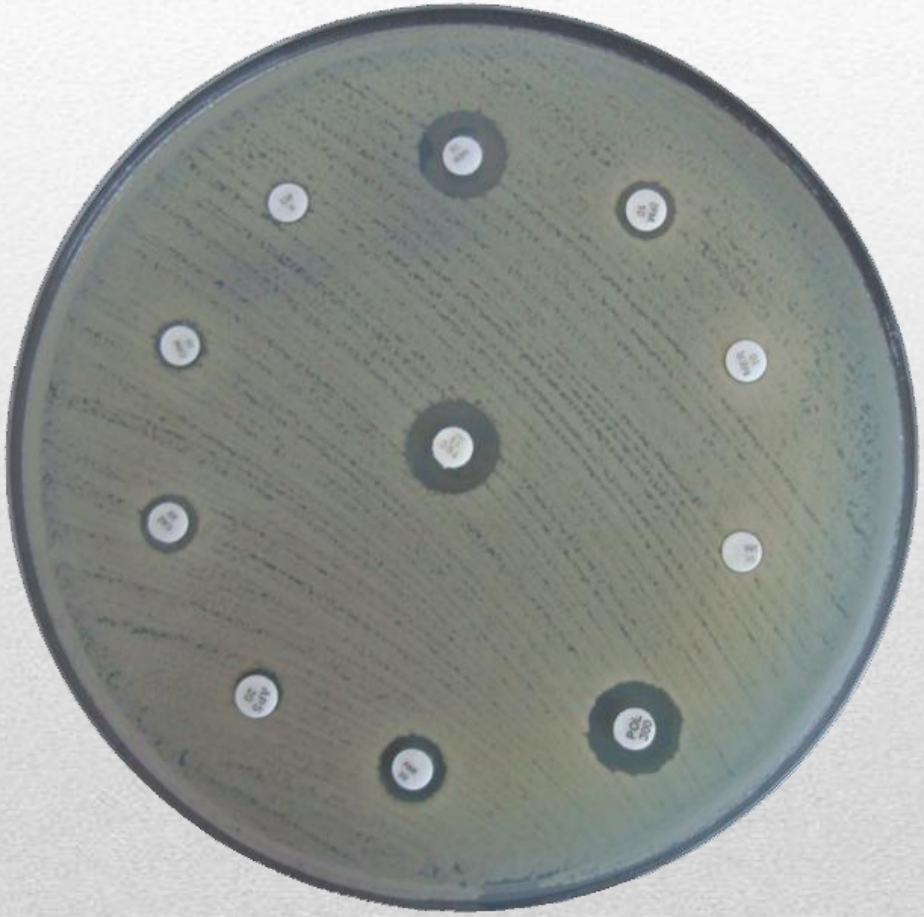
[a] Only carbapenemase types with documented susceptibility to the respective inhibitor are included.

Tzouvelekis et al. CMR, October 2012

Resumindo...

- Detecção de CARBA – tem impacto clínico e epidemiológico
- Detecção deve ser precoce
- Carbapenemase = Tto combinado
- Melhor combinação depende da CIM
- Pontos de corte devem ser validados localmente

3° lugar: *A. baumannii*



Existe correlação entre POL B e COL?

Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09)

- 40625 isolados (*Acinetobacter* spp., *Klebsiella* spp., *E. coli* e *P. aeruginosa*)

Table 1. Antimicrobial activity of polymyxin B and colistin compared with other antimicrobial agents tested against 40625 Gram-negative isolates (SENTRY Antimicrobial Surveillance Program, 2006–09)

Organism (no. tested)/ antimicrobial agent	MIC (mg/L)		Percentage by category[a]	
	50%	90%	susceptible	resistant
Acinetobacter spp. (4686)				
polymyxin B	≤0.5	≤0.5	99.2	0.8
colistin[b]	≤0.5	1.0	98.6	0.9
Klebsiella spp. (9774)				
polymyxin B	≤0.5	≤0.5	98.6	1.4
colistin[b]	≤0.5	≤0.5	98.5	1.5
P. aeruginosa (9130)				
polymyxin B	1	1	99.8	<0.1
colistin[b]	1	1	99.6	0.4
Escherichia coli (17035)				
polymyxin B	≤0.5	≤0.5	99.9	0.1
colistin[b]	≤0.5	≤0.5	99.8	0.2

Gales AC, Jones RN and Sader HS. JAC, 2011

Existe correlação entre metodologias?

Colistin MIC Variability by Method for Contemporary Clinical Isolates of Multidrug-Resistant Gram-Negative Bacilli

Método	Marca
Ágar diluição (AD)	MHA (BBL)
Microdiluição em caldo (BMD)	MHB ajuste de cátion (Difco)
Microdiluição em caldo + polisorbato 80 (BMD-T)	MHB ajuste de cátion (Difco)
Diluição em caldo (TDS)	MHB ajuste de cátion (Difco)
E-test	bioMérieux

- 107 isolados (*A. baumannii*, *K. pneumoniae* e *P. aeruginosa*)

Hindler JA and Humphries RM. JCM, June 2013

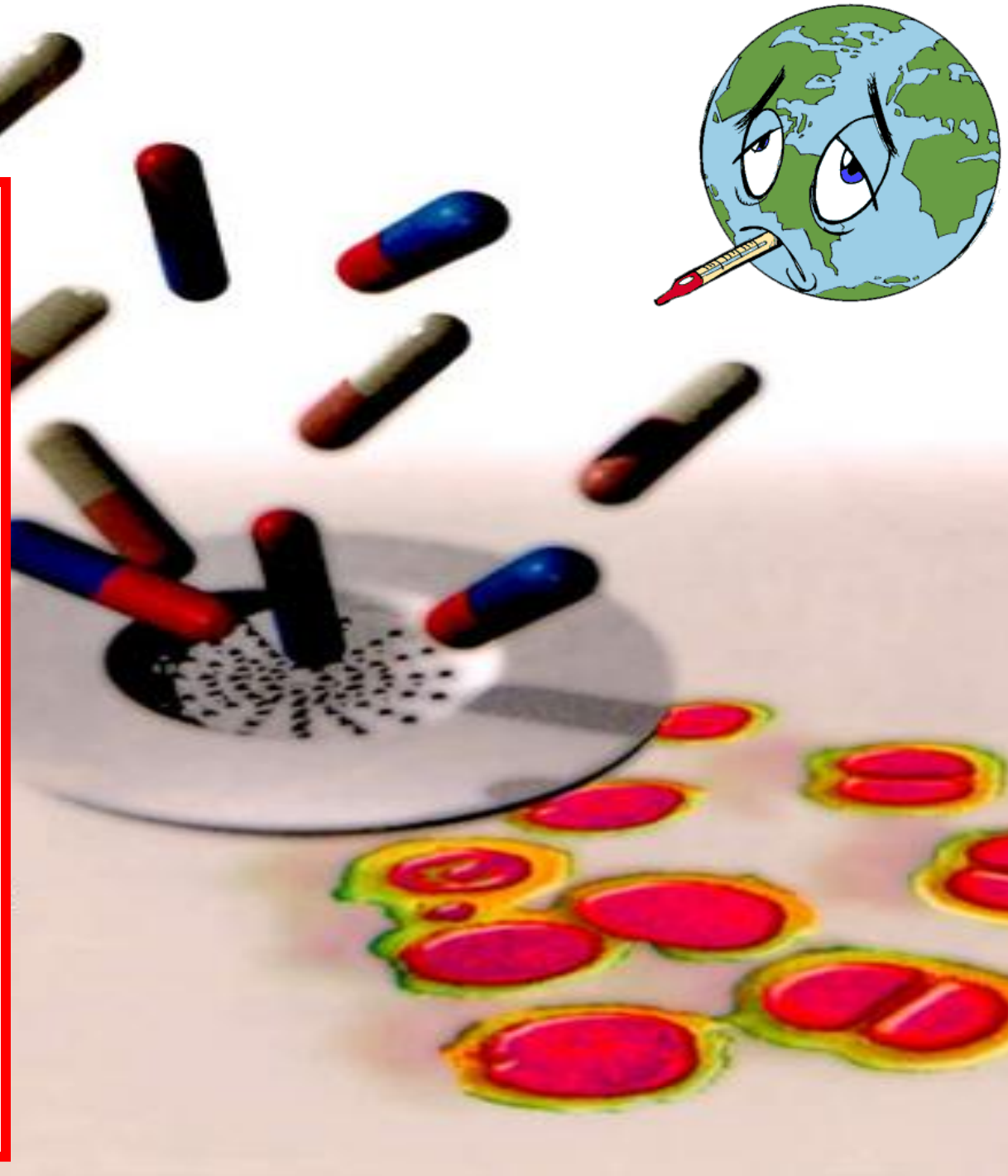
Existe correlação entre metodologias?

Isolate no.[a]	Organism	MIC (µg/ml)[b]					
		Phase I (n = 107)			Phase II (n = 50)		
		BMD-T	TDS	Etest	BMD-T	BMD	AD
1*	*A. baumannii*	4	4	1[b]	0.5	8[c]	0.5
2	*A. baumannii*	8	16	1.5[b]	>8	>8	>16
3	*A. baumannii*	>8	8	2[b]	>8	>8	8
4	*A. baumannii*	8	>16	3	>8	>8	>16
5	*A. baumannii*	>8	16	0.5[b]	ND[d]	ND	ND
6	*A. baumannii*	>8	16	3	ND	ND	ND
7	*A. baumannii*	>8	16	12	ND	ND	ND
7A	*A. baumannii*	2	4[c]	2	2	4[c]	2
8	*K. pneumoniae*	>8	>16	8	>8	>8	>16
9	*K. pneumoniae*	>8	>16	12	>8	>8	>16
10	*K. pneumoniae*	>8	>16	48	>8	>8	>16
11	*K. pneumoniae*	>8	>16	0.5[b]	>8	>8	>16
12	*K. pneumoniae*	>8	>16	8	>8	>8	>16
13	*K. pneumoniae*	4	8	0.5[b]	8	2[b]	4
14*	*K. pneumoniae*	4	8	3	0.25	2	1
15*	*K. pneumoniae*	>8	>16	12	≤0.12	0.5	≤0.25
16	*K. pneumoniae*	8	8	6	ND	ND	ND
17*	*P. aeruginosa*	8	16	3	2	8[c]	4[c]
18	*P. aeruginosa*	2	1	3[c]	4	>8	2[b]
19*	*P. aeruginosa*	4	4	4	2	4[c]	4[c]
20	*P. aeruginosa*	8	8	3	ND	ND	ND
21	*P. aeruginosa*	0.25	1	4[c]	ND	ND	ND
22	*P. aeruginosa*	0.5	0.5	3[c]	0.5	1	1
23	*P. aeruginosa*	2	4[c]	2	2	4[c]	4[c]
24	*P. aeruginosa*	0.5	2	4[c]	ND	ND	ND
25	*P. aeruginosa*	1	1	0.5	1	2	2
No. of VMEs (%)			0 (0)	6 (32)		1 (10)	0 (0)
No. of MEs (%)			2 (2.3)	4 (4.7)		5 (12.5)	3 (7.5)
% EA			83	61		34	80
% CA			98	91		88	94

Hindler JA and Humphries RM. JCM, June 2013

O PROBLEMA CONTINUA

- Prescrições incorretas
  - Infecções virais
- Falhas no CIH
- Tratamento descontínuo
- Utilização ATB ração animal
  - Cadeia alimentar / contaminam o solo
- Globalização
  - Disseminação de cepas resistentes pelo mundo



Obrigada pela atenção!!!

jussarakp@ig.com.br