Como Tratar Enterobactérias Resistentes a Carbapenêmicos

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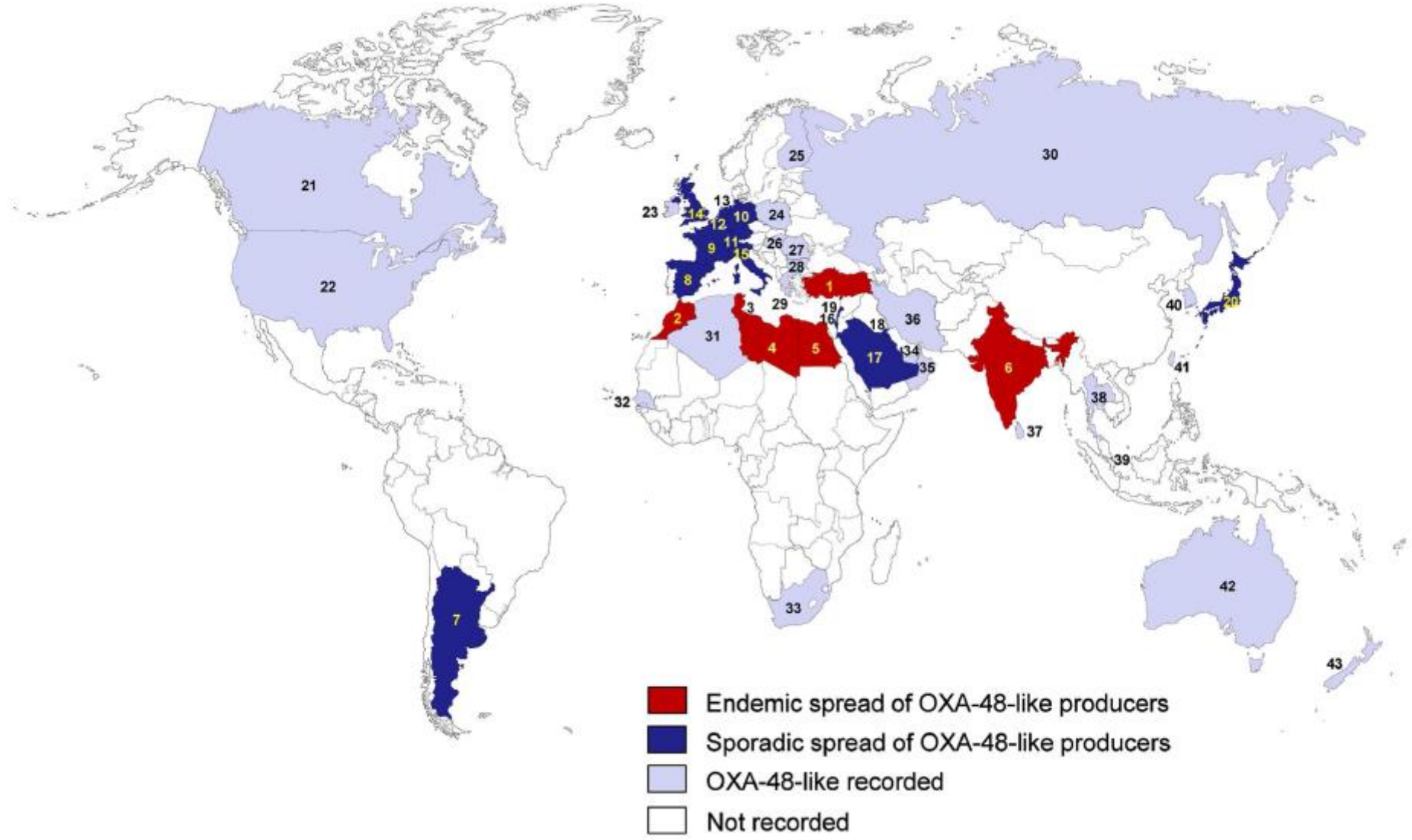
Resistência aos carbapenêmicos

- β-lactamases com fraca hidrólise CBP (ESBLs / AmpC)
  + alterações de permeabilidade
- Carbapenemases +/- alterações de permeabilidade

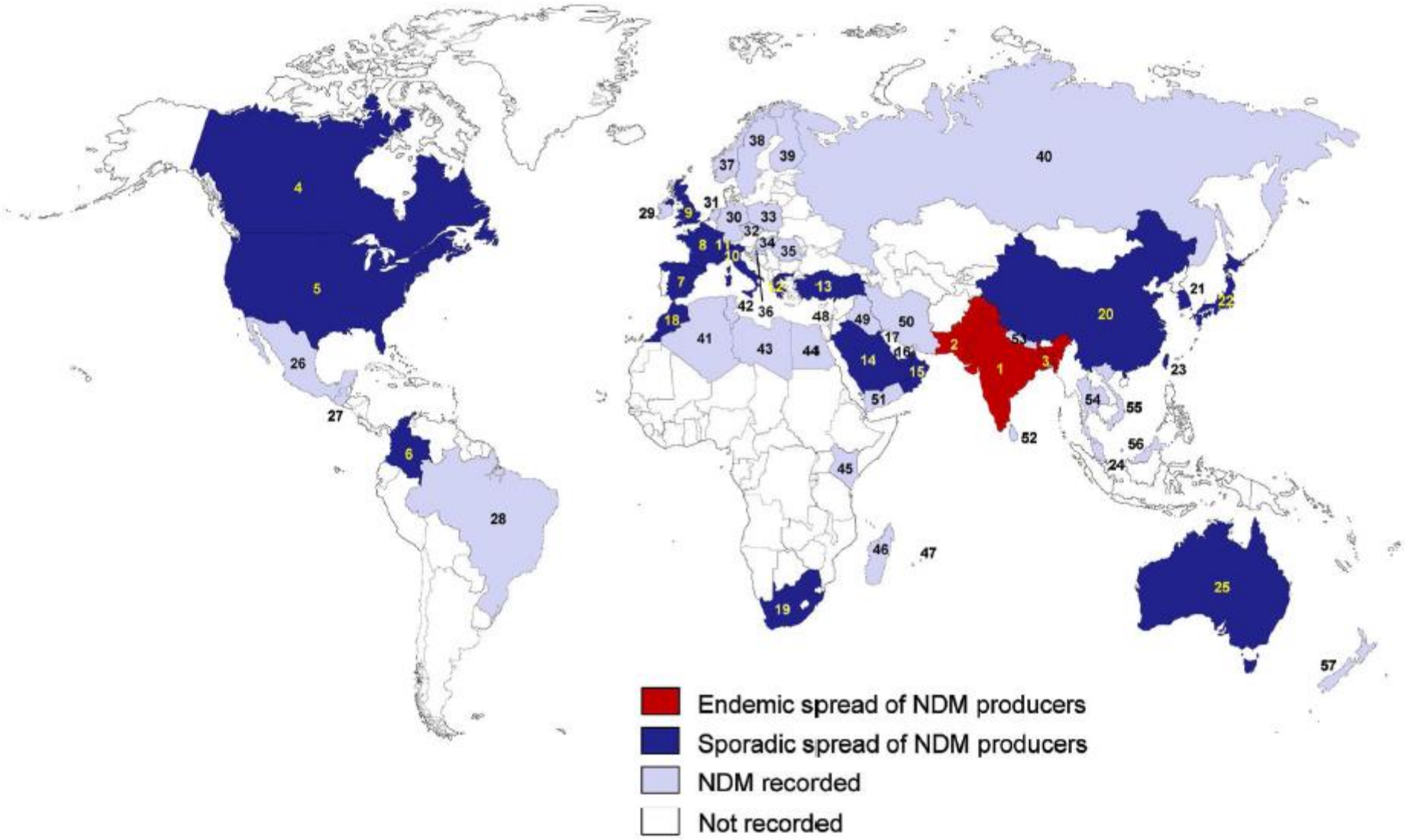
TABLE 1 Characteristics of *K. pneumoniae* strains that produce carbapenemases

Enzyme types (class) and examples	Spectrum of activity	Inhibitor(s)
MBLs (B): NDM-1, IMP, VIM	Penicillins, cephalosporins, cephamycins, carbapenems	Metal chelators, e.g., EDTA, dipicolinic acid
KPCs (A): KPC-2, -3, others	Penicillins, cephalosporins, cephamycins, carbapenems	Clavulanic acid (weak), tazobactam(weak), boronic acid, avibactam
OXA-β-lactamases (D): OXA-48, OXA-181, OXA-204, OXA-232	Penicillins, temocillin, β-lactamase inhibitor combinations, carbapenems (weak)	NaCl

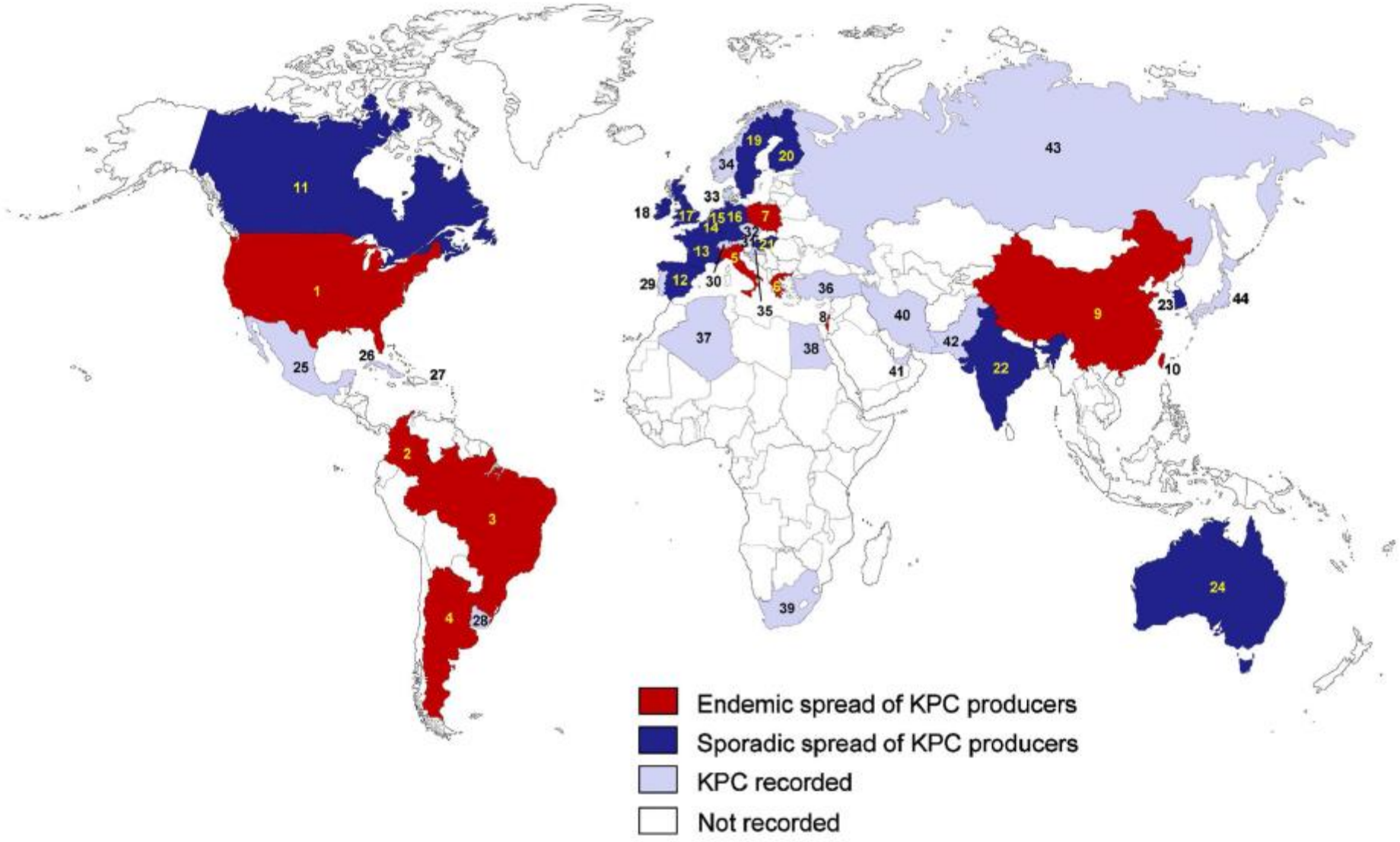
Pitout *et al*. Antimicrob Agents Chemother, 2015



Lee *et al*. Front Microbiol, 2016



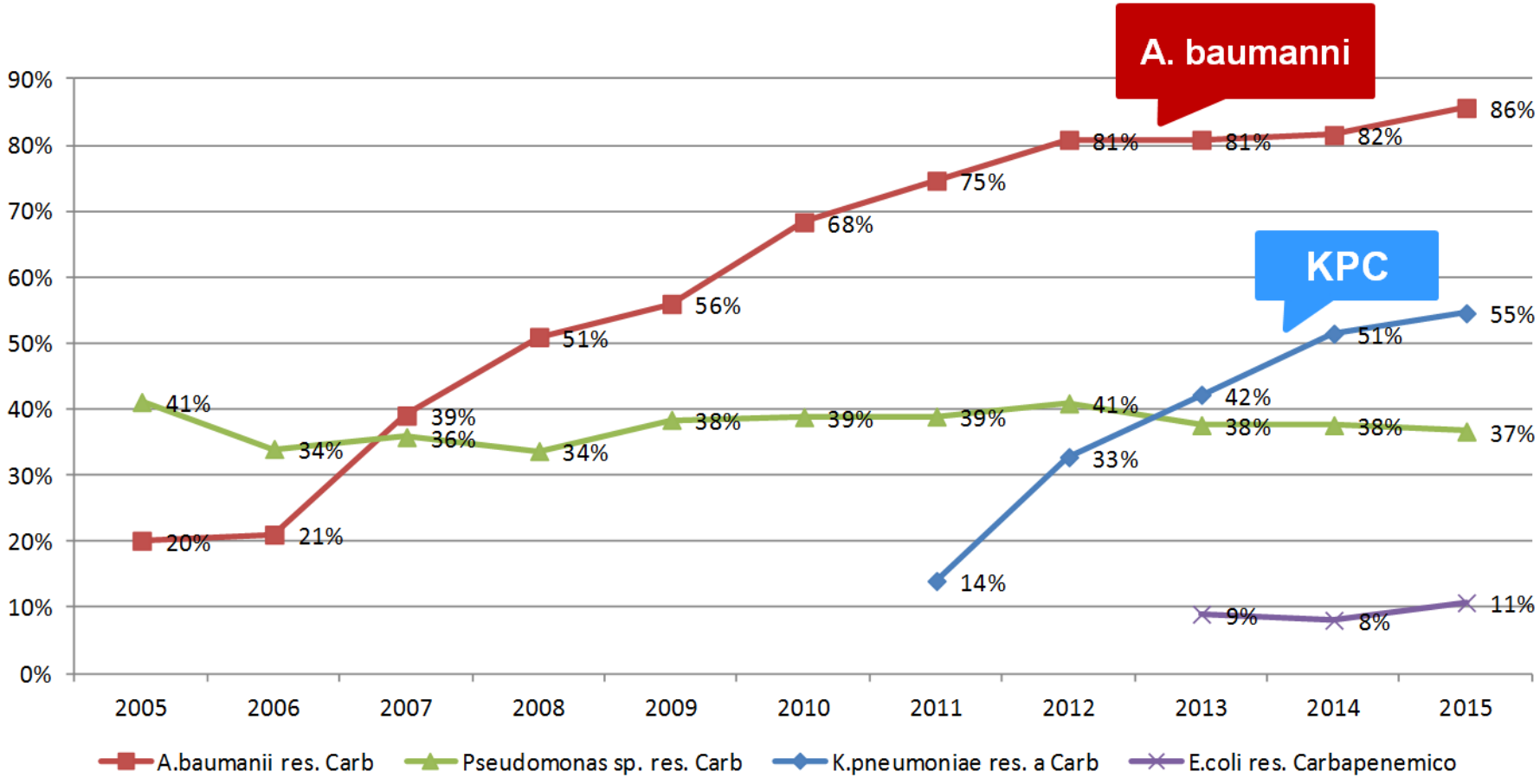
Lee *et al*. Front Microbiol, 2016



Lee *et al*. Front Microbiol, 2016

Evolução da Resistência aos carbapenêmicos nas UTI do ESP 2005 a 2015

Divisão de Infecção Hospitalar



Impacto da resistência ao carbapenêmico

- Mortalidade 2x > que nas bacteremias por *CSE*
  - 48% *CRE* x 22% *ESBL* x 17% *KpnS*
- Mortalidade atribuída à resistência: 26 – 44%
  - > probabilidade de terapia empírica inadequada
  - Uso de terapias menos efetivas que o carbapenêmico
  - Produção de carbapenemase relacionada a pior prognóstico
    - Fatores de virulência?
    - > MIC carbapenêmicos?

Daikos *et al*. Int J Antimicrob Agents, 2007

Daikos *et al*. Antimicrob Agents Chemother, 2009

Chang *et al*. J Microbiol Immunol Infect, 2011

Mouloudi *et al*. Infect Control Hosp Epidemiol, 2010

Patel *et al*. Infect Control Hosp Epidemiol, 2008

Falagas *et al*. J Antimicrob Chemother, 2007

Ben-David *et al*. Clin Microbiol Infect, 2012

Gaviria *et al*. MMWR, 2011

Schwaber *et al*. Antimicrob Agents Chemother, 2008

Falagas *et al*. Emerg Infect Dis, 2014

Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* Bacteremia

83 pacientes com bacteremia monomicrobiana por *CRE*

Table 4. Fourteen-Day Mortality for Patients With Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* (CP-CRE) Compared With non-CP-CRE Bacteremia

Covariate	Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratioa (95% CI)	*P* Value
Carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* bacteremia	3.20 (1.06–9.61)	.04	4.92 (1.01–24.81)	.05
Pitt bacteremia score ≥4	9.13 (2.39–34.86)	.001	11.89 (2.38–59.30)	.005
Active empiric antibiotic therapy	.79 (0.27–2.29)	.67	2.46 (0.53–11.48)	.25
Active directed antibiotic therapy	.17 (0.04–0.72)	.01	0.10 (0.004–2.22)	.14
Days of combination antibiotic therapy	.89 (0.79–1.00)	.07	0.73 (0.59–0.93)	.01
Polymixin therapy administered	4.61 (1.16–18.3)	.03	5.57 (1.07–28.96)	.04
Diabetes	3.12 (0.99–9.84)	.05	3.42 (0.62–19.07)	.16
Immunocompromised	.45 (0.14–1.40)	.17	–	–
Carbapenem therapy administered	.82 (0.27–2.52)	.74	–	–
Meropenem minimum inhibitory concentration ≥16 μg/mL	1.40 (0.38–5.01)	.61	–	–

Tamma *et al*. Clin Infect Dis, 2017

Comparing the Outcomes of Patients With Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* Bacteremia

Impacto da produção de carbapenemase

- Restrito a MIC ≤ 4µg/mL, com terapia empírica ativa
  - Mortalidade 14d: aOR: 3,39 (*P* = .08)
  - > Mortalidade 30d: aOR: 3,79 (*P* = .04)

- Recorrência em 30d (terapia adequada e controle do foco)
  - 9 (38%) x 3 (8%) – (*P* = .003)

Tamma *et* al. Clin Infect Dis, 2017

Tratamento de ERC

Monoterapia	Mortalidade	Pacientes (estudos)
Carbapenêmico	9 – 50%	29 (3)*
Tigeciclina	0 – 53%	38 (4)**
Colistina	33 – 57%	102 (8)
Gentamicina	6,3 – 80%	26 (3)***

*25/29 S a CBP
**1 Estudo: pacientes em UTI: 80% mortalidade
***19/26 ITU não complicada

Terapia combinada	Mortalidade	Pacientes (estudos)
Tige + colistina	0 – 30%	51 (4)*
Tige + genta	0 – 50%	15 (2)
Carbap + Colistina	0 – 67%	25 (4)** ***
Colistina + gentamicina	40 – 61%	30 (3)

*1 estudo só em UTI e VIM-1: 64%
**16/25 carbap S.
***67% mortalidade em estudo de TOS e UTI

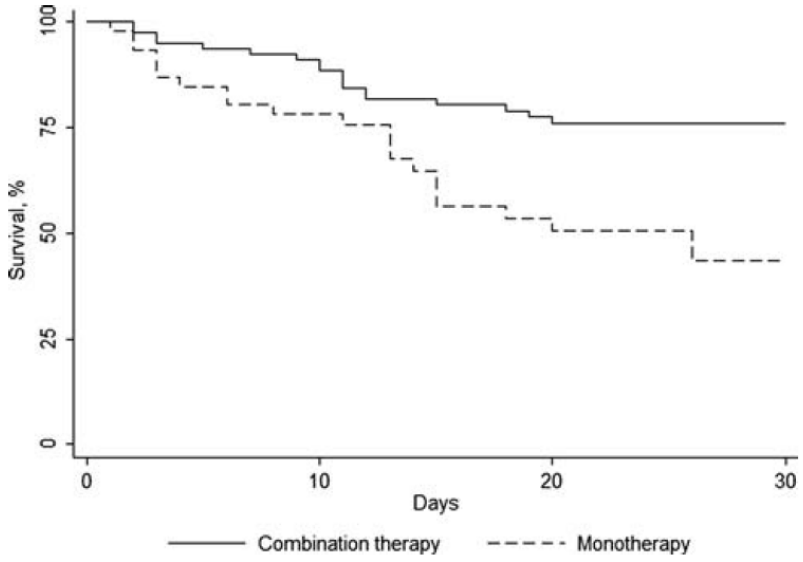
Falagas *et* al. Antimicrob Agents Chemother, 2014

Tratamento de ERC

- Tratamento ideal indefinido
  - Séries de casos
  - Múltiplos focos
  - Diferentes mecanismos de resistência
  - Diferentes perfis de susceptibilidade
- Estratégia depende do tipo de carbapenemase
- Controle do foco é essencial, especialmente em infecções intra-abdominais

Pitout *et* al. Antimicrob Agents Chemother, 2015

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy



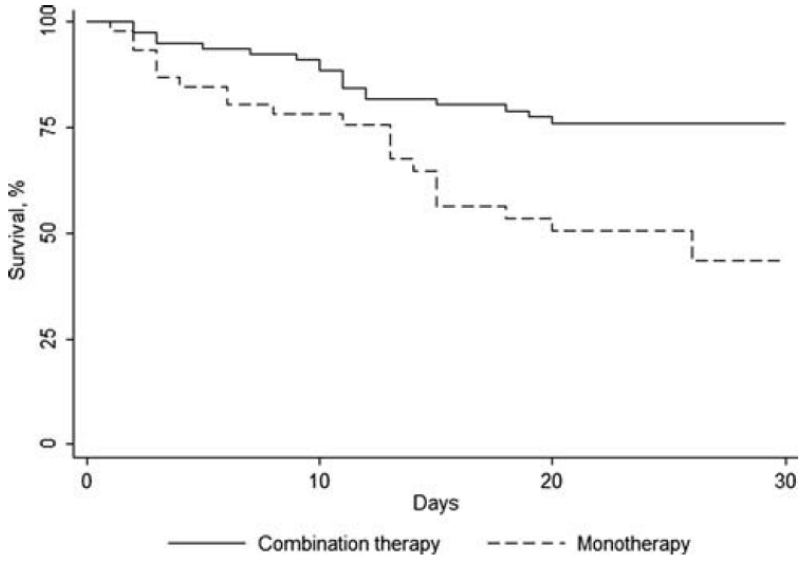
N=125
Mortalidade: 41,6%
(34,1% x 54,3%) *P* = .02

Table 3. Multivariate Analysis of Risk Factors for Mortality in Patients With Bloodstream Infection Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

Variable	*P* Value	OR (95% CI)
Presentation with septic shock	.008	7.17 (1.65–31.03)
Inadequate initial antimicrobial treatment	.003	4.17 (1.61–10.76)
High APACHE III score	<.001	1.04 (1.02–1.07)
Postantibiogram therapy with tigecycline + colistin + meropenem	.01	0.11 (.02–.69)

Tumbarello *et* al. Clin Infect Dis, 2012

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy



N=125
Mortalidade: 41,6%
(34,1% x 54,3%) *P* = .02

Table 4. Outcomes of the 36 Bloodstream Infections Treated With Combination Therapy Including Meropenem Stratified by Meropenem Minimum Inhibitory Concentration

		No. (%)	
Meropenem MIC (mg/L)	Total	Nonsurvivors	Survivors
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	1 (25)	3 (75)
≥16	17	6 (35.2)	11 (64.7)
Total	36	9 (25)	27 (75)

Tumbarello *et* al. Clin Infect Dis, 2012

Terapia combinada

- Preferencialmente com carbapenêmico * KPC
- Associação com:
  - Polimixina B / colistina
  - aminoglicosídeo
  - Tigeciclina
  - Outros: rifampicina, fosfomicina
  - Duplo carbapenêmico

Doi *et* al. Semin Resp Crit Care Med, 2015

Polimixina B / colistina

Polimixina B

- Droga ativa
- Dose de ataque discutível
- Pouca eliminação renal
- Sem ajuste para Ins renal

Colistina

- Pró droga
- Dose de ataque
- Eliminação renal
- Ajuste para Ins renal

Desenvolvimento de resistência

KPC +

Comunitárias – mcr-1

Aumento incidência de infecções por *Serratia spp* e *Proteus spp*

Nefrotoxicidade

Polimixina B / colistina

- Retrospectivo, 3 centros – SP
- 15% bacteremia 2ª IAB
- 92% Kpn

TABLE 3. Multivariate analysis of factors associated with 30-day mortality in patients with infections caused by KPC-producing Enterobacteriaceae in three large teaching hospitals (2009–2013)

	OR	95% CI	p
All infections (n = 118)			
Renal failure at end of treatment	2.96	1.18–7.44	0.02
Urinary tract infection	0.34	0.11–1.06	0.06
Use of polymyxin	3.07	1.22–7.72	0.02
Older age	1.03	1.01–1.05	0.05
Bacteremic infections (n = 78)			
Renal failure at end of treatment	3.83	1.23–11.96	0.02
Older age	1.04	1.004–1.07	0.04
Use of polymyxin	5.50	1.63–18.54	0.006

KPC, *Klebsiella pneumoniae* carbapenemase.

de Oliveira *et* al. Clin Microbiol Infect, 2015

Multicentre open-label randomised controlled trial to compare colistin alone with colistin plus meropenem for the treatment of severe infections caused by carbapenem-resistant Gram-negative infections (AIDA): a study protocol

Trial registration number: NCT01732250 and 2012-004819-31; Pre-results.

Yaakov Dickstein,[1] Leonard Leibovici,[2,3] Dafna Yahav,[3,4] Noa Eliakim-Raz,[3,4] George L Daikos,[5] Anna Skiada,[5] Anastasia Antoniadou,[6] Yehuda Carmeli,[7] Amir Nutman,[3,7] Inbar Levi,[7] Amos Adler,[8] Emanuele Durante-Mangoni,[9] Roberto Andini,[9] Giusi Cavezza,[9] Johan W Mouton,[10,11] Rixt A Wijma,[10] Ursula Theuretzbacher,[12] Lena E Friberg,[13] Anders N Kristoffersson,[13] Oren Zusman,[2,3] Fidi Koppel,[1] Yael Dishon Benattar,[1] Sergey Altunin,[14†] Mical Paul,[1,14] the AIDA consortium

TRIAL STATUS

To date, 240 patients, or 67% of the planned total, have been recruited within 25 months (of a planned 36), including 178 in Israel, 40 in Greece and 22 in Italy. The centre in Italy began participation more than a year after the start of trial. An additional 204 patients (175 in Israel, 27 in Greece and 2 in Italy) have been recruited into the observational trial.

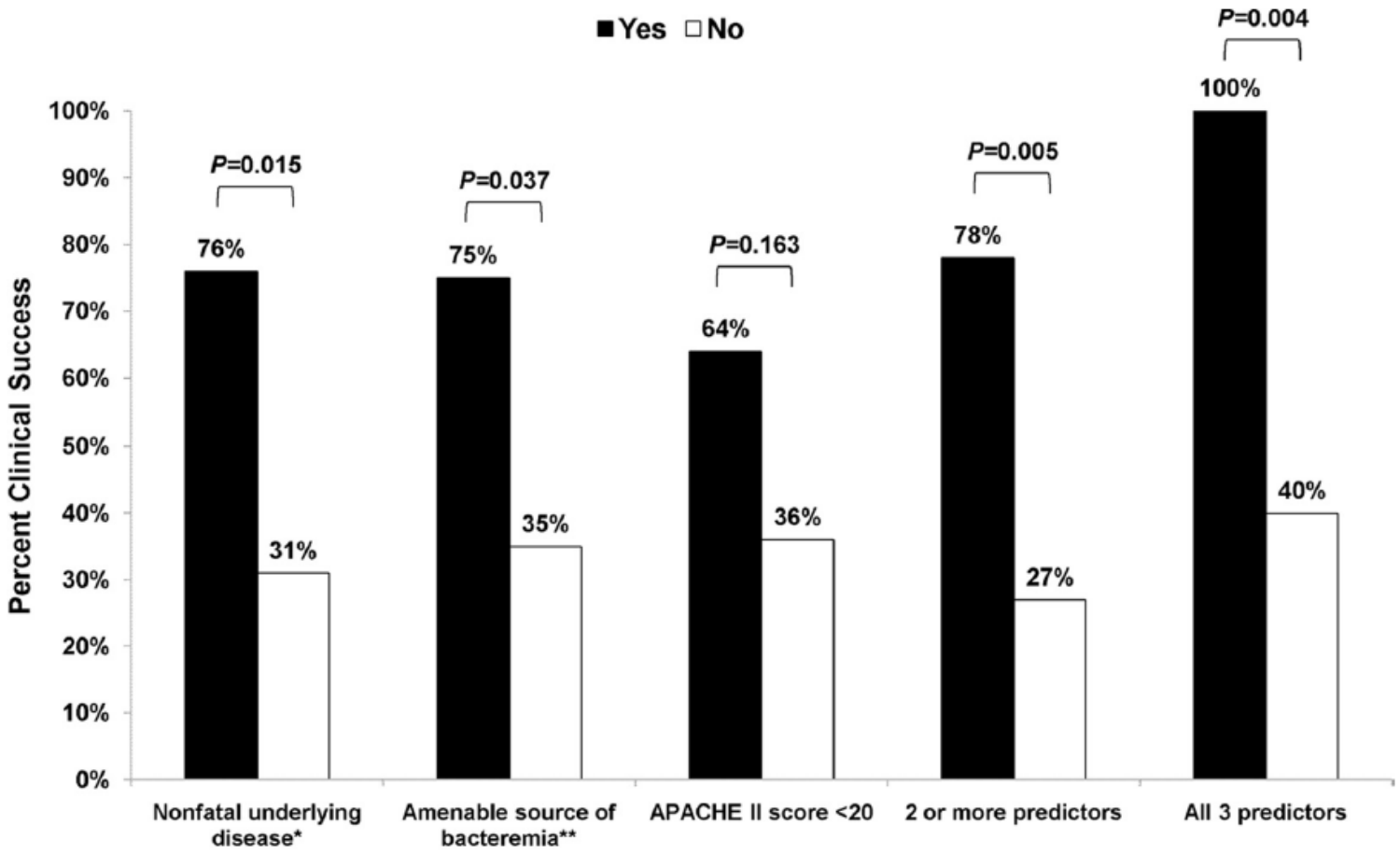
Dickstein *et* al. BMJ Open, 2016

Aminoglicosídeo

- Bacteremia – Kpn R carbapenêmico
- Retrospectivo – 33 casos (14 - 2ª infecção intra-abdominal)
- Mortalidade 14d: 22%, sucesso clínico 54%
- Sem diferença entre mono X combinado (tige ou doripenem)
- 36% nefrotoxicidade

Shields *et* al. Antimicrob Agents Chemother, 2016

Aminoglicosídeo

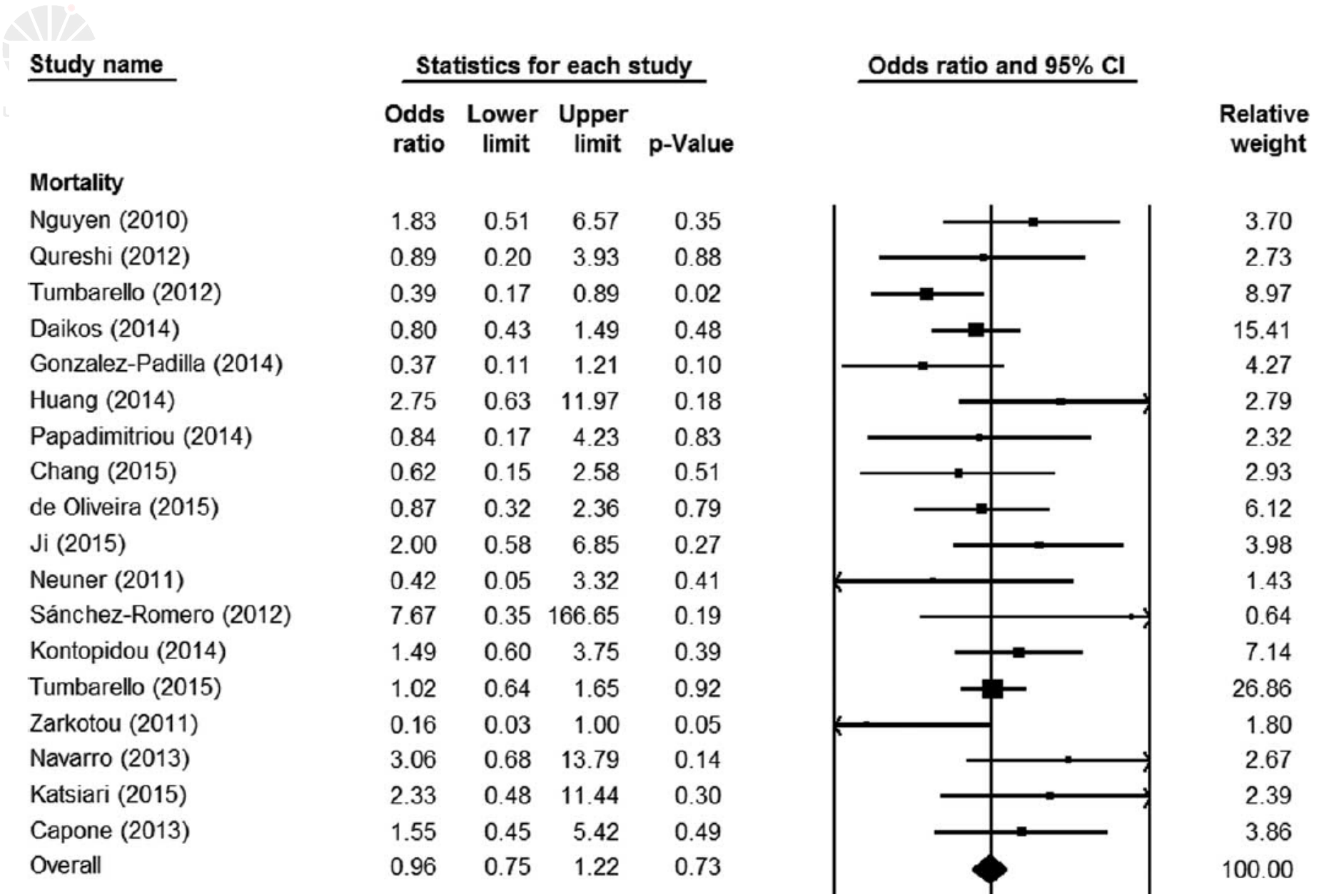


Shields *et* al. Antimicrob Agents Chemother, 2016

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

Ni *et* al. Medicine (Balt), 2016



Ni *et* al. Medicine (Balt), 2016

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

TABLE 3. Subgroup Analysis of Mortality With Tigecycline Monotherapy or Combination Therapy Versus the Controls for Treatment of Carbapenem-Producing *Enterobacteriaceae* and CRE Infections in Controlled Studies

Variables	Mortality Type	Studies, No. (Patients, No.)	Mortality of Tigecycline Compared With Control OR (95% CI); *P*	Heterogeneity of Studies
Monotherapy vs control	30-day	9 (427)	1.19 (0.72–1.96); $P=0.49$	$I^2=7.04\%$; $Q=8.61$; $P=0.38$
	14-day	3 (401)	1.14 (0.74–1.77); $P=0.55$	$I^2=0\%$; $Q=1.77$; $P=0.41$
	Infection-related	3 (51)	1.45 (0.34–6.26); $P=0.62$	$I^2=0\%$; $Q=0.44$; $P=0.80$
Combination vs control	30-day	8 (519)	0.59 (0.39–0.88); $P=0.01$	$I^2=4.18\%$; $Q=7.31$; $P=0.40$
	14-day	2 (106)	1.60 (0.57–4.52); $P=0.38$	$I^2=27.35\%$; $Q=1.38$; $P=0.24$
	Infection-related	3 (90)	1.04 (0.14–7.89); $P=0.97$	$I^2=68.87\%$; $Q=6.43$; $P=0.04$

Ni *et* al. Medicine (Balt), 2016

Tigecycline Treatment for Carbapenem-Resistant *Enterobacteriaceae* Infections

A Systematic Review and Meta-Analysis

TABLE 4. Subgroup Analysis of Mortality Using Different Tigecycline Regimens to Treat Carbapenem-Producing *Enterobacteriaceae* and Carbapenem-Resistant *Enterobacteriaceae* Infections

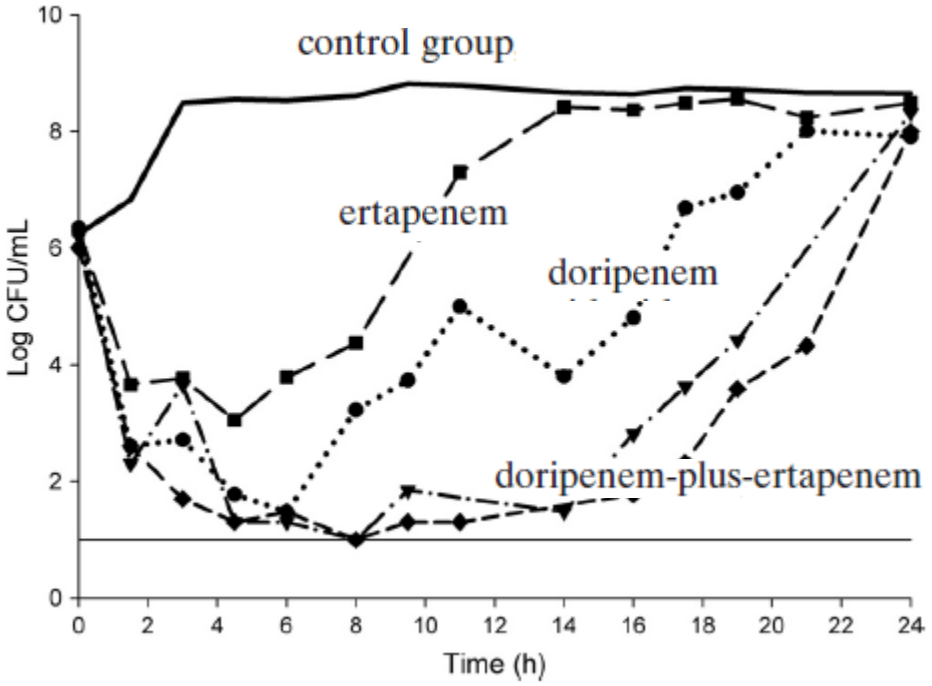
Variables	Mortality Type	Studies, No. (Patients, No.)	Mortality Difference OR (95% CI); *P*	Heterogeneity of Studies Included
Monotherapy vs combination	30-day	9 (317)	1.83 (1.07–3.12); $P=0.03$	$I^2=0\%$; $Q=7.81$; $P=0.45$
	Infection-related	3 (59)	1.75 (0.33–9.27); $P=0.51$	$I^2=46.34\%$; $Q=3.73$; $P=0.16$
	14-day	2 (42)	1.00 (0.34–2.99); $P=1.00$	$I^2=0\%$; $Q=0.65$; $P=0.42$
	ICU	2 (62)	1.10 (0.11–10.67); $P=0.94$	$I^2=46.29\%$; $Q=1.86$; $P=0.17$
Double combination* vs triple combination†	30-day	8 (205)	2.18 (1.03–4.63); $P=0.04$	$I^2=4.31\%$; $Q=6.27$; $P=0.39$
	Infection-related	4 (58)	0.63 (0.16–2.54); $P=0.51$	$I^2=0\%$; $Q=1.05$; $P=0.59$
High dose vs standard dose‡	30-day	2 (47)	2.25 (0.55–9.24); $P=0.26$	$I^2=0\%$; $Q=0.02$; $P=0.90$
	ICU	2 (62)	12.48 (2.06–75.43); $P=0.006$	$I^2=0\%$; $Q=0.22$; $P=0.64$

CI = confidence interval; OR = odds ratio.
* Double combination: tigecycline in combination with 1 other antibiotic.
† Triple combination: tigecycline in combination with 2 other antibiotics.
‡ High dose: 200 mg initially, followed by 100 mg every 12 h; standard dose: 100 mg initially, followed by 50 mg every 12 h.

Ni *et* al. Medicine (Balt), 2016

Duplo carbapenêmico

- KPC tem maior afinidade pelo ertapenem – “droga suicida”



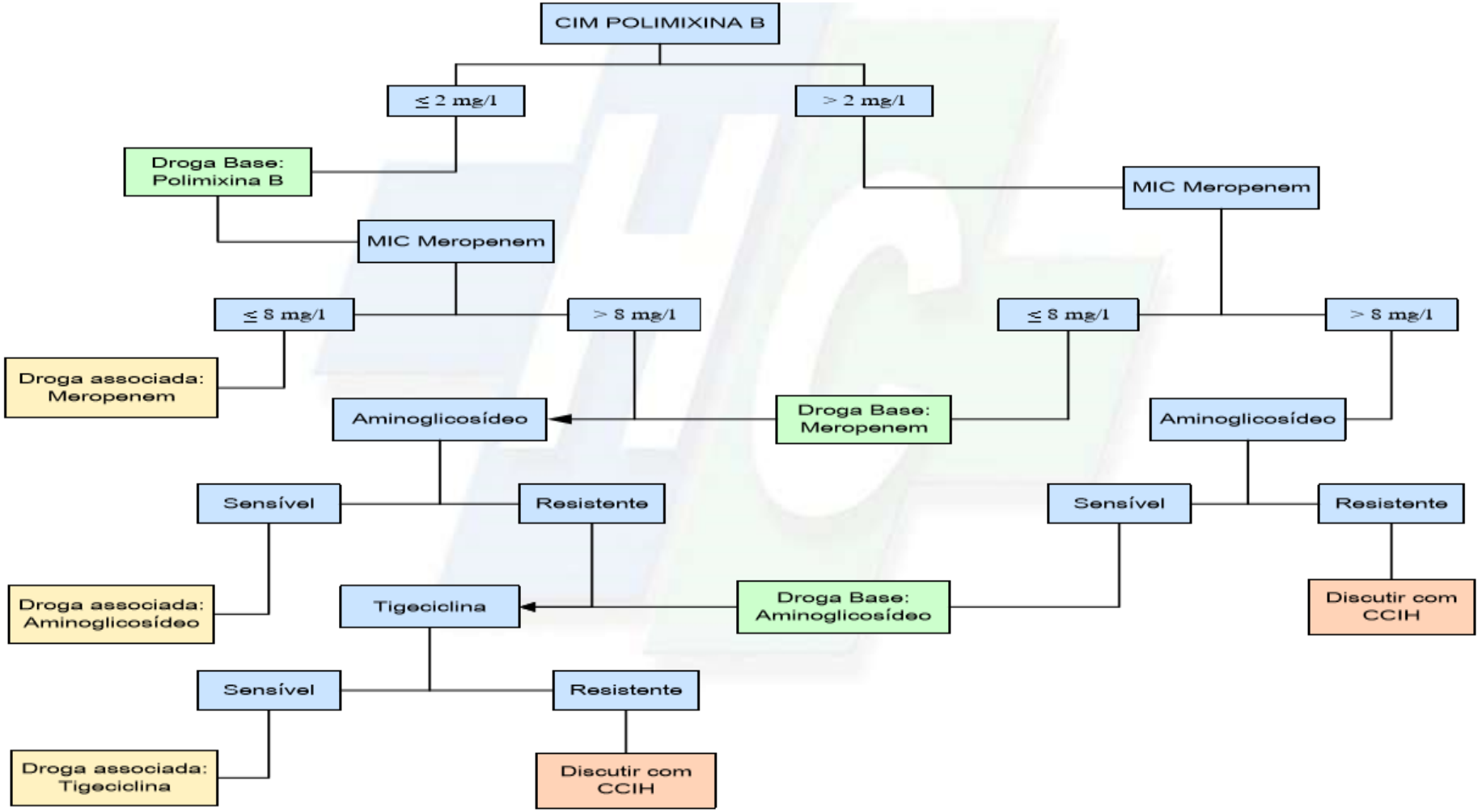
Bullik *et* al. Antimicrob Agents Chemother, 2011

Duplo carbapenêmico

- Erta + dori/mero – n=3
  * KPC + pan droga resistentes
  – 3/3 sucesso – todas bacteremias 2ª ITU

- Erta + dori/meropenem – n=18
  * Sem identificação KPC / sem MIC
  – 7/18 sucesso clínico
  – 0/2 nas infecções intra-abdominais
  – 1/2 nas bacteremias 2ª infecção intra-abdominal

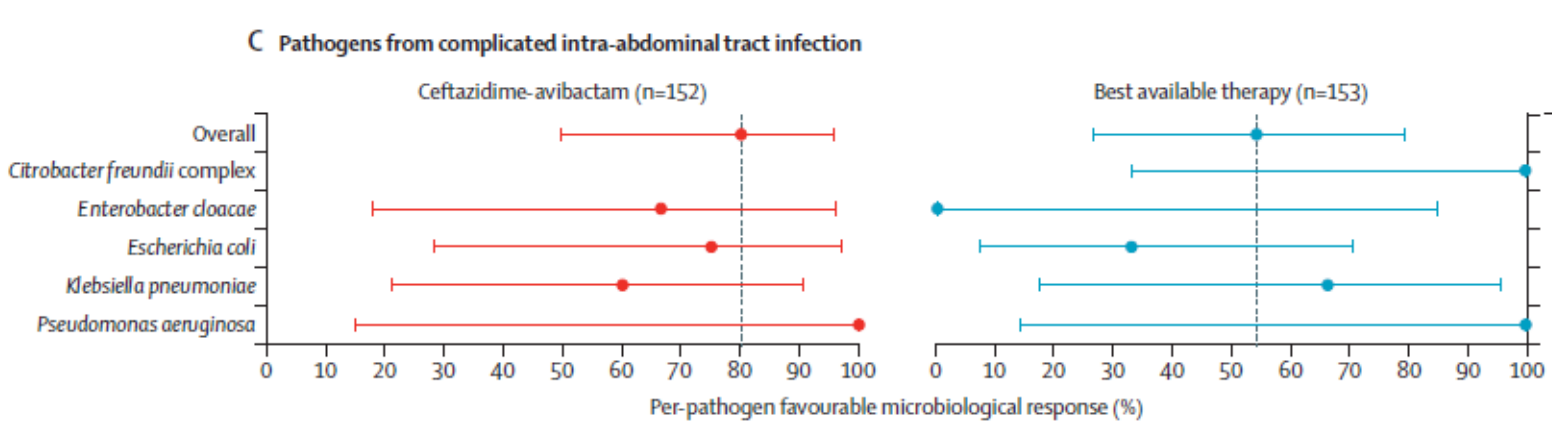
Giamarellou *et* al. Antimicrob Agents Chemother, 2013
Cprek *et* al. Antimicrob Agents Chemother, 2016


CIM POLIMIXINA B
≤ 2 mg/l
> 2 mg/l
Droga Base: Polimixina B
MIC Meropenem
MIC Meropenem
≤ 8 mg/l
> 8 mg/l
≤ 8 mg/l
> 8 mg/l
Droga associada: Meropenem
Aminoglicosídeo
Droga Base: Meropenem
Aminoglicosídeo
Sensível
Resistente
Sensível
Resistente
Droga associada: Aminoglicosídeo
Tigeciclina
Droga Base: Aminoglicosídeo
Discutir com CCIH
Sensível
Resistente
Droga associada: Tigeciclina
Discutir com CCIH

Novas drogas

- Novos inibidores β-lactamases
  - Ceftazidima/avibactam
  - Aztreonam/avibactam
  - Imipenem/relebactam
- Novos β-lactâmicos
  - Ceftolozane/tazobactam
- Novos aminoglicosídeos
  - Plazmomicina
- Fluorociclina
  - Eravaciclina

Ceftazidima/avibactam



	Ceftazidime-avibactam		Best available therapy	
	n/N	%	n/N	%
Overall	8/10	80%	6/11	55%
Citrobacter freundii complex	0/0	NC	2/2	100%
Enterobacter cloacae	2/3	67%	0/1	0%
Escherichia coli	3/4	75%	2/6	33%
Klebsiella pneumoniae	3/5	60%	2/3	67%
Pseudomonas aeruginosa	1/1	100%	1/1	100%

Carmeli *et* al. Lancet Infect Dis, 2016

Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation β-Lactam/β-Lactamase Inhibitor Combinations

Table 1. Comparative In Vitro Inhibitory Activity of Tazobactam and Avibactam Against Selected β-Lactamases

			Inhibited by	
Enzymes	Class	Substrates	Tazobactam	Avibactam
TEM-1, TEM-2, SHV-1	A	Penicillins, early cephalosporins	Yes	Yes
TEM-3, SHV-2 CTX-M-14	A	Extended-spectrum cephalosporins, monobactams	Yes	Yes
KPC-2, KPC-3	A	Broad spectrum including carbapenems	No	Yes
IMP-1, NDM-1, VIM-1	B	Broad spectrum including carbapenems, but not monobactams	No	No
Escherichia coli AmpC	C	Cephalosporins	High concentrations	Yes
OXA-48	D	Carbapenems	No	Yes

Van Duin *et* al. Clin Infect Dis, 2016

Avibactam

Antimicrobial[a]	% susceptibility with resistance mechanism shown		
	KPC (108)	NDM (32)	OXA-48 group (14)
β-Lactams and β-lactam–β-lactamase inhibitor combinations			
ATM	2	9	14
AZA	100	94	100
CAZ	2	0	14
CZA	100	0	93

ATM, aztreonam; AZA, aztreonam-avibactam; CAZ, ceftazidime; CZA, ceftazidime-avibactam

Vasoo *et* al. Antimicrob Agents Chemother, 2015

Organism subset (*n*) and agent[a]	% susceptible[b]
All *Enterobacteriaceae* (38,266)	
Ceftazidime	76.9
Ceftazidime-avibactam[c]	99.5
Aztreonam	75.7
Aztreonam-avibactam[c]	NA
KPC-positive *Enterobacteriaceae*	
All (557)	
Ceftazidime	3.9
Ceftazidime-avibactam	97.5
Aztreonam	1.3
Aztreonam-avibactam	NA

Kazmierczak *et* al. Antimicrob Agents Chemother, 2016

Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

TABLE 2 MICs (in μg/ml) of carbapenems in 33 isolates for which susceptibility was reported quantitatively

Organism and antibiotic[a]	No. of isolates with MIC of:			
	<2	2	4 to 8	>8
Enterobacteriaceae				
Imipenem (n = 29)	1	2	2	24
Meropenem (n = 27)	0	1	2	24
P. aeruginosa				
Imipenem (n = 2)	0	0	0	2
Meropenem (n = 1)	0	0	0	1

Temkin al. Antimicrob Agents Chemother, 2016

Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

TABLE 3 Characteristics of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI

Characteristic	Value (n = 38)[a]
Infection characteristics	
Organism and carbapenemase	
Klebsiella pneumoniae	
KPC	22
OXA-48	12
Klebsiella oxytoca (KPC)	1
Escherichia coli (OXA-48)	1
Pseudomonas aeruginosa	2
Hospital-acquired infection	34 (89.5)
Bacteremia	26 (68.4)
Polymicrobial infection	11 (29.0)
Life-threatening infection (high risk of death within 30 days)	23 (60.5)
Antibiotics before CAZ-AVI	
Received antibiotics before CAZ-AVI for this infection	36 (94.7)
Days of antibiotic treatment before CAZ-AVI, median (IQR)	13 (7–31)
No. of antibiotics before CAZ-AVI, median (IQR)	3 (3–4)
Other treatments before CAZ-AVI	
Surgery to remove the source of infection	16 (42.1)
Removal of foreign body involved in infection	9 (23.7)
Clinical status at start of CAZ-AVI treatment	
Mechanical ventilation	14 (36.8)
Vasopressor support	17 (44.7)
Unconscious	12 (31.6)

Temkin al. Antimicrob Agents Chemother, 2016

Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

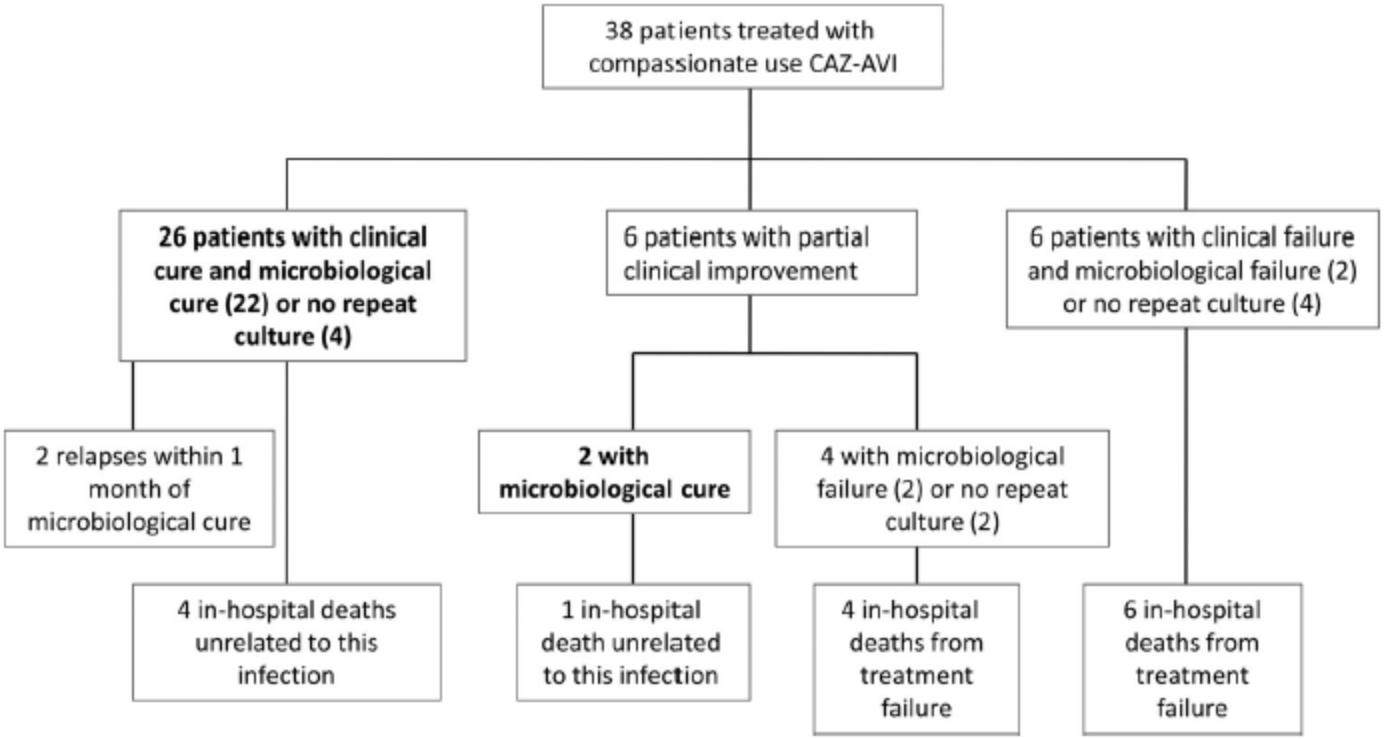


FIG 1 Outcomes of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI.

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Resumo

- Resistência a carbapenêmico eleva o risco de tratamento inadequado e morte
- Recomendações baseadas em séries de casos, especialmente bacteremias
- Terapia combinada apresenta indícios de melhor resposta
- Carbapenêmico deve fazer parte do esquema sempre que possível
- Uso de polimixina pode estar relacionado a maior mortalidade
- Tigeciclina deve ser usada em terapia combinada e, possivelmente em doses elevadas
- Duplo carbapenêmico pode ser efetivo
- Ceftazidima/avibactam é possivel alternativa para tratamento de KPC