Clinical Assessment of Susceptibility Data

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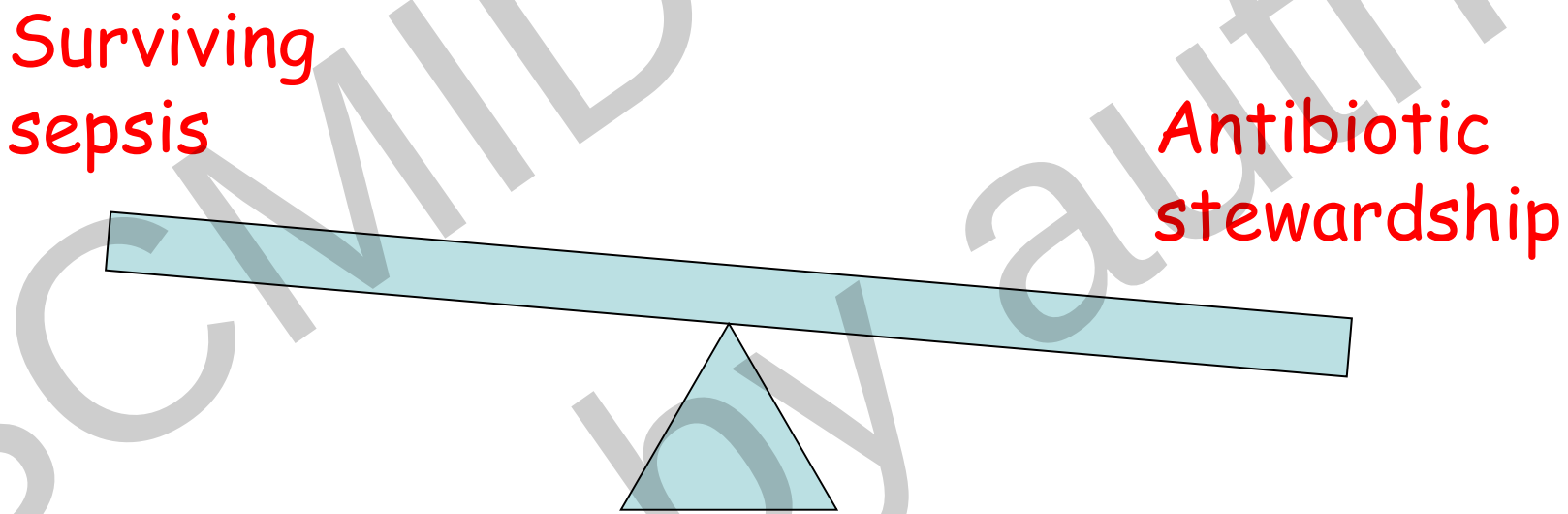
Disclosures

- No conflicts of interests

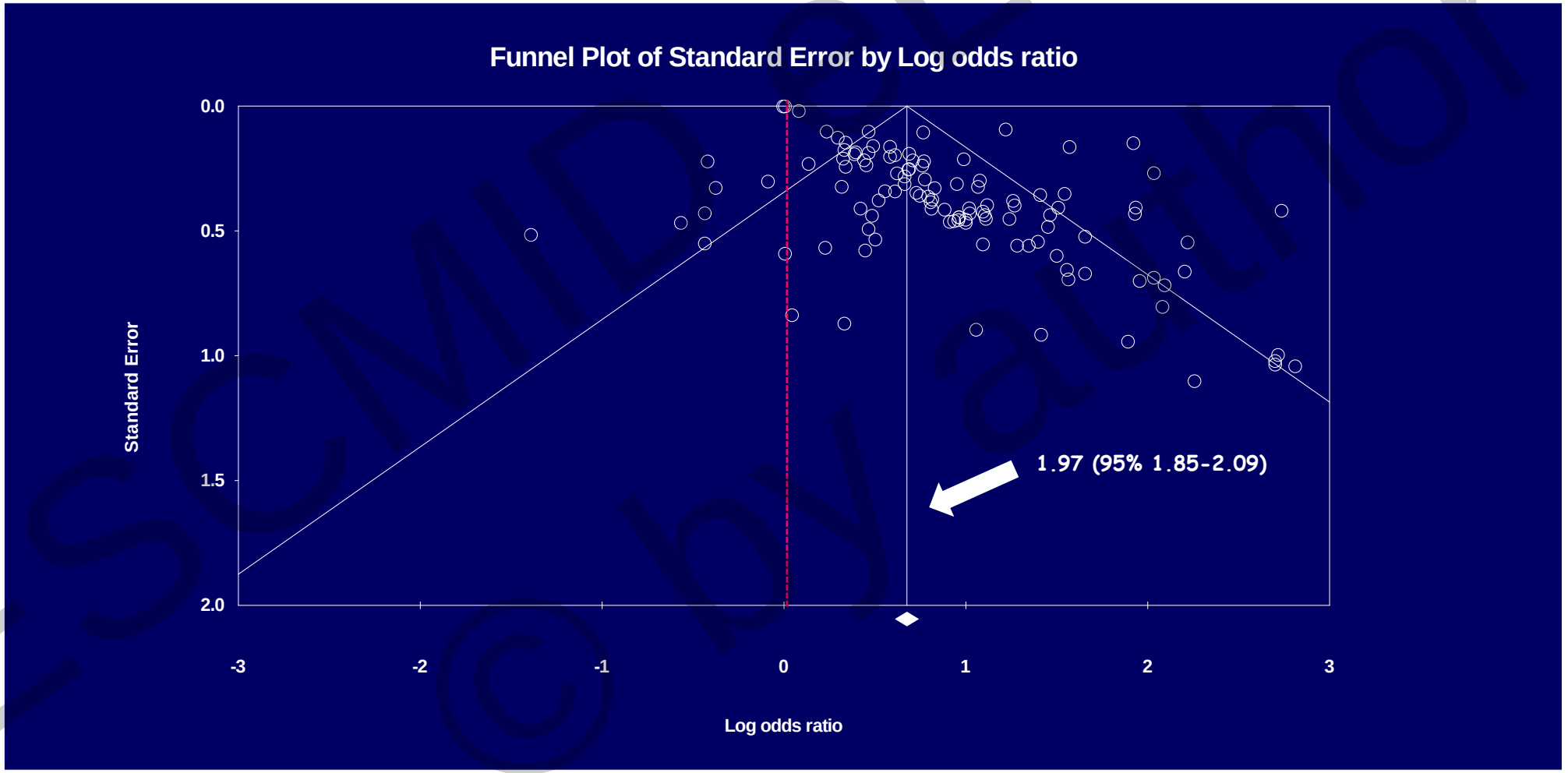


Appropriate empirical antibiotic treatment

- Systematic review and meta-analysis
- Adjusted association between appropriate empirical antibiotic treatment and all-cause mortality
- Observational studies published between 1975-2008 (prospective) and between 2009-2015 (retrospective or prospective)
- "Appropriateness" defined microbiologically using contemporary CLSI/ EUCAST definitions

Paul et al. Antimicrob Agents Chemother 2010 + update

Adjusted association between appropriate empirical antibiotic treatment and all-cause 30-day mortality



OR=0.13 OR=0.34 OR=1 OR=2.7 OR=7.4

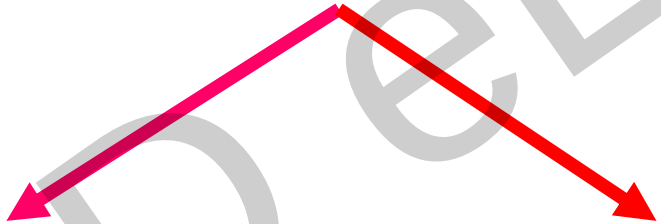
Potential association modifiers

Modifier	Categories/ units	N studies	Ratio of odds ratios (95% CI)	P value
None	All studies	114	1.97 (1.85-2.09)	
Bacteremia	All patients bacteremic <100% with bacteremia	75 39	2.21 (1.91-2.57) 1.52 (1.42-1.64)	<0.001
Source of infection	All with VAP/ HAP Mixed sourced	19 95	2.72 (2.09-3.55) 1.86 (1.74-1.98)	0.007
Septic shock	Per 1% increase of patients with septic shock	80	1.003 (0.998-1.009)	NS
Place of acquisition	Intensive care unit Community or hospital	28 86	2.79 (2.07-3.74) 1.77 (1.66-1.87)	0.003
Pathogen	All with Gram-negative Mix/ other	41 73	2.54 (2.1-3.07) 1.81 (1.69-1.94)	0.001
Year start	Per 1 year increase	113	0.989 (0.97-1.008)	NS

Systematic review summary

- Nearly all studies show an association between inappropriate empirical antibiotic treatment and mortality
  - Certainly for Gram-negative bacterial infections
- All patient subgroups/ characteristics identified showed the association
- Perhaps the sicker the patient the stronger the association

What do we learn?

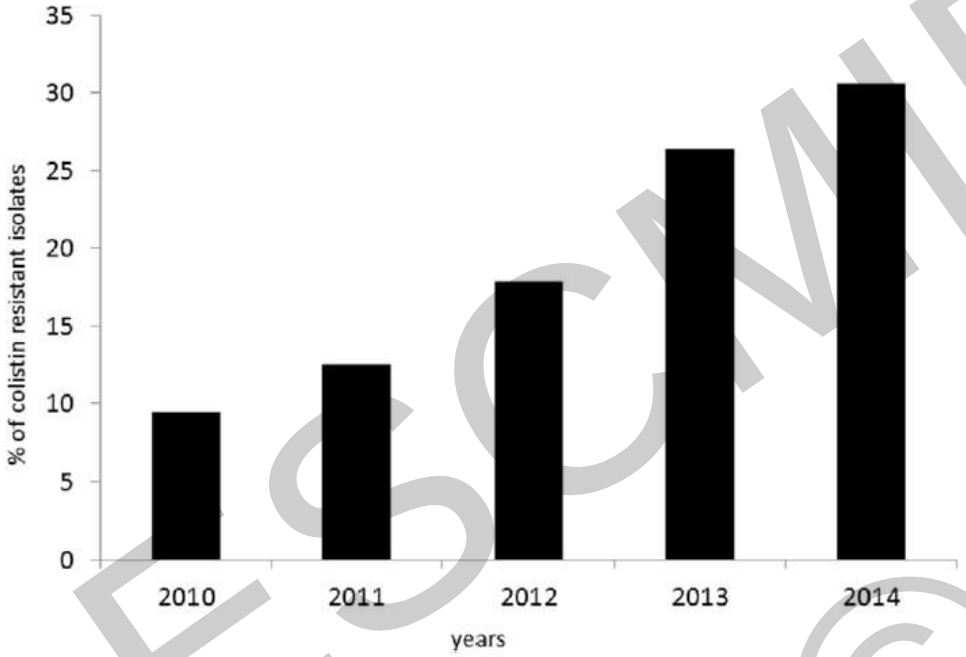


Taken at face value	More suspiciously: all breakpoint definitions work the same?
A very strong signal that breakpoints are associated with the outcome of sepsis	Unaccounted for selection bias, explaining why patients given inappropriate empirical antibiotic treatment die more

Who is carbapenem-resistant?

Meropenem	FDA	CLSI 2010	CLSI 2013	EUCAST 2016
S	≤4	≤4	≤1	≤2
I	8	8	2	4-8
R	≥16	≥16	≥4	≥16

What's next?



Giacobbe et al. Clin Microbiol Infect 2015

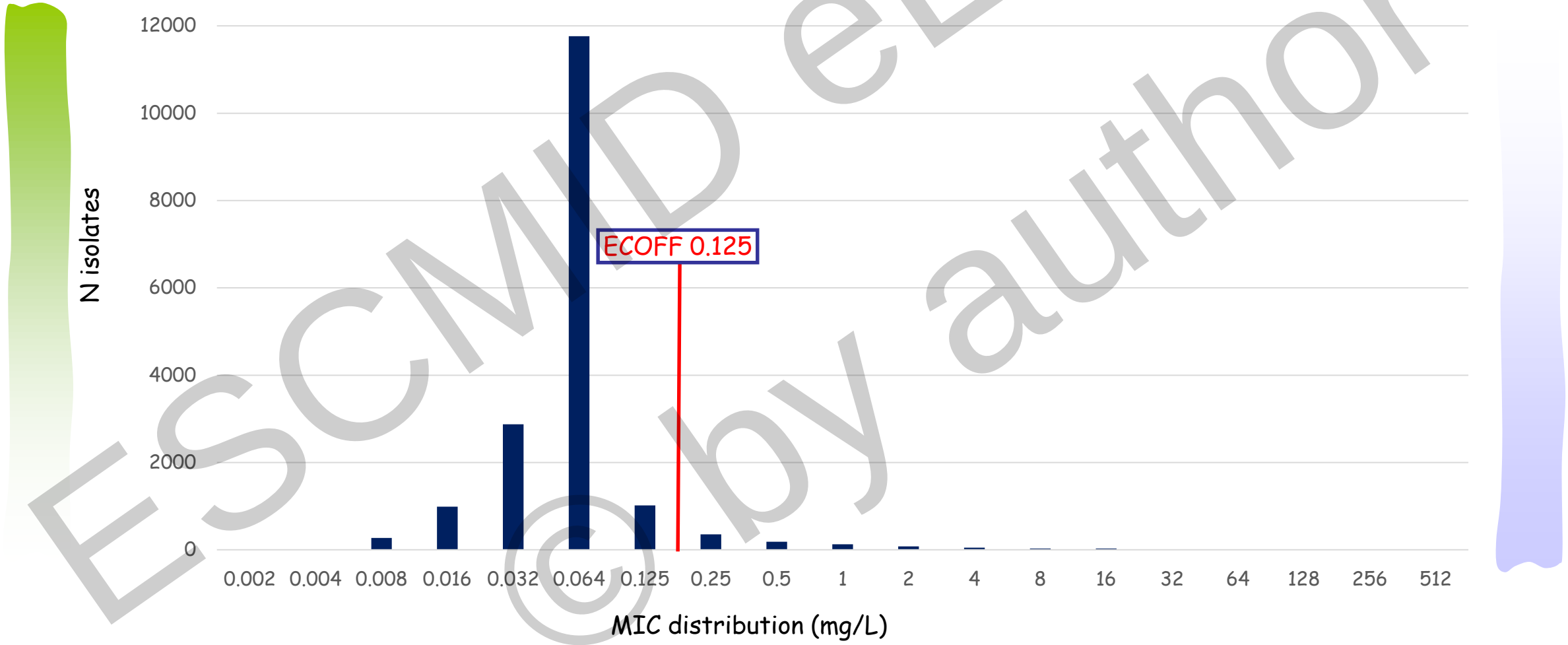
Control group and risk factors	OR (95% CI)	p
Control group A (patients without KPC-Kp infection)[b]		
Previous colistin administration	24.51 (8.75–68.67)	<0.001
Previous colonization with KPC-Kp	18.71 (8.05–43.51)	<0.001
Previous ≥3 hospitalization	5.32 (2.48–11.38)	<0.001
Charlson score ≥3	2.84 (1.52–5.29)	0.001
Neutropenia	2.72 (1.02–7.23)	0.04
Control group B (patients with BSI due to colistin-susceptible KPC-Kp)[c]		
Previous colistin administration	6.88 (3.55–13.34)	<0.001
Previous colonization with KPC-Kp	2.40 (1.46–3.97)	0.001
Charlson score ≥3	2.97 (1.74–5.06)	<0.001

http://www.eucast.org/clinical_breakpoints/

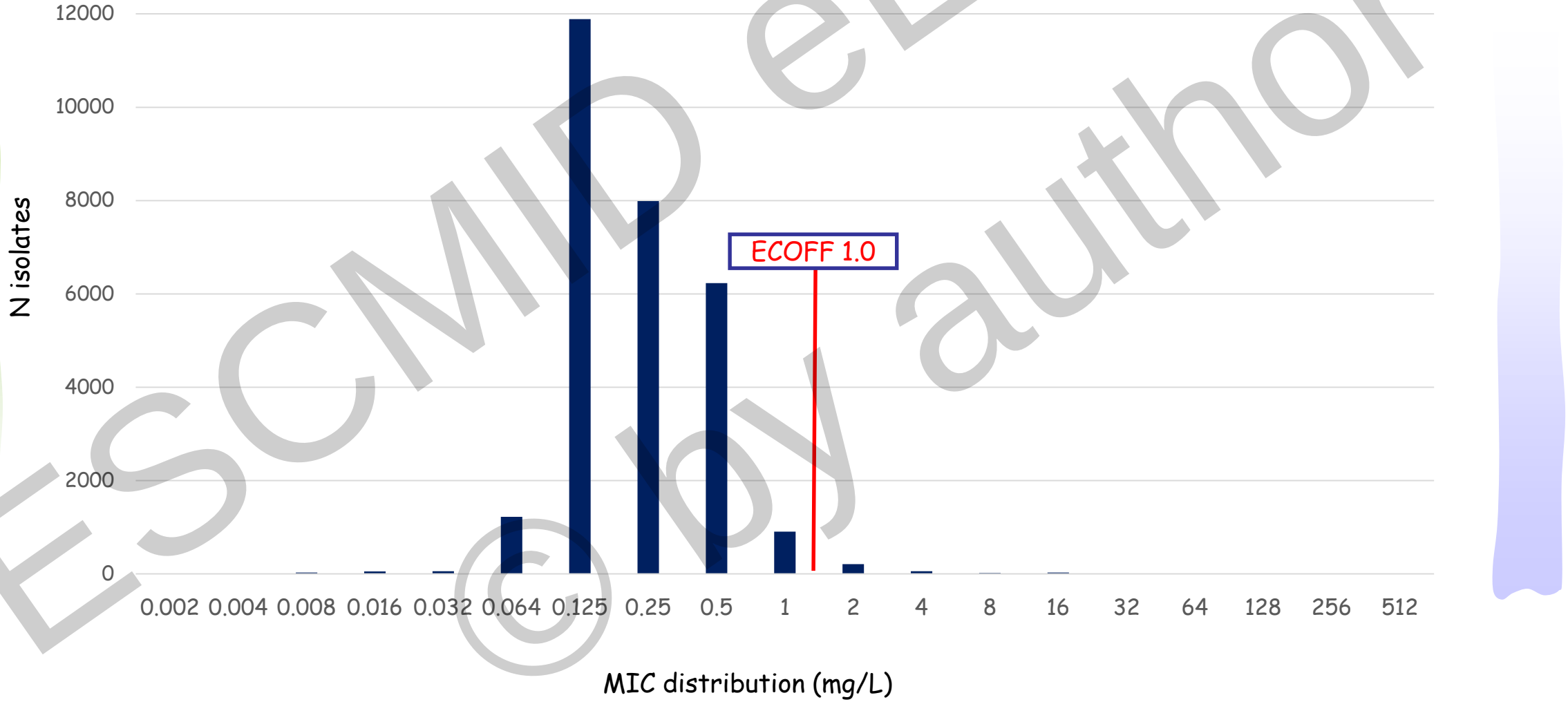
Carbapenems	MIC breakpoint (mg/L)	
	S ≤	R >
Doripenem	1	2
Ertapenem	0.5	1
Imipenem	2	8
Meropenem	2	8

The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases). Some isolates that produce carbapenemase are categorised as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorisation of susceptibility. Carbapenemase detection and characterisation are recommended for public health and infection control purposes.

K. pneumoniae: meropenem MIC distributions and ECOFF



K. pneumoniae: imipenem MIC distributions and ECOFF



Setting clinical breakpoints

Breakpoints have been determined using Pk/Pd data to achieve a 2 log drop in viable Gram-negative organisms in animal model infections. This requires that unbound drug concentrations exceed the MIC 40-50% of the time (fT>MIC 40-50%)

European Committee on Antimicrobial Susceptibility Testing. Setting breakpoints for new antimicrobial agents, EUCAST SOP 1.2, 2016 and Meropenem, Rationale for the EUCAST clinical breakpoints, version 1.5 1st June 2009. http://www.eucast.org

Pre-change clinical study

- Some have speculated that current CLSI guidelines' suggested thresholds are too high and that clinical success is more likely if the MIC value is <1 mg/L for certain organisms.
- The primary goal of this study was to determine if a clinical mortality breakpoint existed for carbapenems in patients treated with carbapenems for Gram-negative bloodstream infections.

Esterly et al. Antimicrob Agents Chemother 2012

Study design and methods

- Retrospective cohort study
- Single center, Chicago, 2005-2008
- Included adults treated with a carbapenem for bacteremia cause by *Acinetobacter baumannii*, *Pseudomonas aeruginosa* or ESBL-producing enterobacteraceae
- Analyzed in-hospital mortality based on bacteria MICs
- CART analysis to define a breakpoint

Results

Node 0 All Patients		
	%	n
Survived	72.5	50
Died	27.5	19
Total	100	69

Imipenem MIC

Node 1 MIC 1, 2 mcg/mL		
	%	n
Survived	83.9	47
Died	16.1	9
Total	100	56

p≤0.01

Node 2 MIC 4, 8, 16 mcg/mL		
	%	n
Survived	23.1	3
Died	76.9	10
Total	100	13

Multivariate analysis	aOR (95% CI)
Imipenem MIC ≥4 mg/L	27.9 (3.82-202.9)
ICU at onset	5.75 (1.26-26.3)
Liver failure	5.87 (1.14-30.2)
UTI source	0.14 (0.017-1.1)

Who is carbapenem-resistant?

Meropenem	FDA	CLSI 2010	CLSI 2013	EUCAST 2016
S	≤4	≤4	≤1	≤2
I	8	8	2	4-8
R	≥16	≥16	≥4	≥16

Post-change clinical study

- There is a limited amount of data evaluating clinical outcomes with the use of carbapenems for treatment of *Enterobacteriaceae* infection with MICs of 2 to 8 mg/liter.
- The primary goal of this study was to determine if a difference in clinical outcomes existed between patients treated with a carbapenem for *Enterobacteriaceae* infections with MICs of <1 mg/L and MICs of 2 to 8 mg/L

Patel JL, Nagel JL. J Clin Microbiol 2015

Study design and methods

- Retrospective matched cohort study
- Single center, Michigan, 2009-2013
- Included adults infected by enterobacteriaceae with MIC<16 mg/L, treated with a carbapenem
- Carbapenem MICs 2-8 mg/L matched 1:1 to MIC ≤1 mg/L
  - Age +/- 10 yrs.
  - Charlson score +/- 3
  - Source of infection
  - Pathogen
  - Intensive care unit (ICU) status
- All-cause 30-day morality assessed

Results

Demographic or characteristic	Value	
	MIC of ≤1 mg/liter (n = 18 patients)	MIC of 2–8 mg/liter (n = 18 patients)
Mean age ± SD (yrs)	59 ± 13.6	61 ± 13.0
No. (%) of males	12 (66.7)	7 (38.9)
Mean Charlson comorbidity index ± SD	6.6 ± 2.2	6.1 ± 2.6
No. (%) of patients by culture sources		
Blood	3 (16.7)	3 (16.7)
Respiratory	6 (33.3)	6 (33.3)
Intra-abdominal	3 (16.7)	3 (16.7)
Urinary	4 (22.2)	4 (22.2)
Wound	2 (11.1)	2 (11.1)
No. (%) of patients with MIC of:		
≤1 mg/liter	18 (100.0)	0
2 mg/liter	0	10 (55.6)
4 mg/liter	0	5 (27.8)
8 mg/liter	0	3 (16.7)
Mean duration of therapy ± SD (days)	11 ± 8.5	11 ± 9.4
No. (%) of patients on concomitant antibiotics[a]	9 (50.0)	14 (77.8)
One additional agent	7 (38.9)	8 (44.4)
Two additional agents	2 (11.1)	6 (33.3)

Outcomes by carbapenem MIC

MIC 2 deaths 4/10 (40%)
MIC 4 deaths 2/5 (40%)
MIC 8 deaths 1/3 (33%)

Outcome	Value		*P* value
	MIC of ≤1 mg/liter	MIC of 2–8 mg/liter	
No. of patients with 30-day mortality/total number of patients (%)	1/18 (5.6)	7/18 (38.9)	0.04
Mean total hospital length of stay ± SD, in days	34.4 ± 25	57.6 ± 45	0.06
Mean ICU length of stay ± SD, in days	21.7 ± 19	56.6 ± 44	<0.01
No. of patients with 30-day hospital readmission/total number of patients (%)	3/17 (17.6)	3/11 (27.3)	0.65

Taipei, Japan, single center, 2012-2013

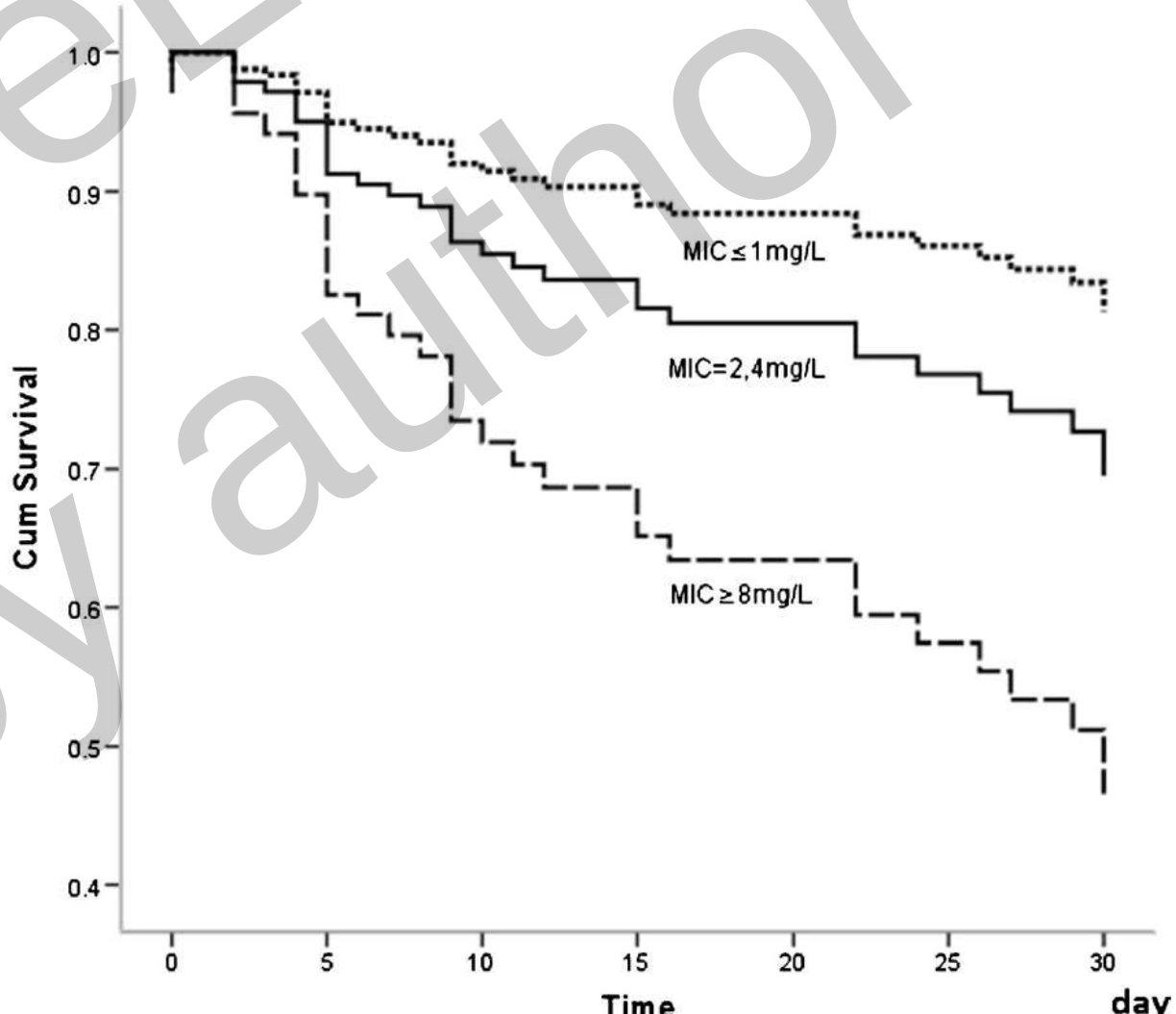
- Included patients with clinically significant infections caused by *K. pneumoniae* with an imipenem or meropenem MIC ≥ 2 mg/L

Imipenem MIC (mg/L)	N patients	Univariate OR for 14-day mortality	Multivariate aOR for 14-day mortality
>4	39	6.26 (0.72-54.41)	
≥8	30	2.87 (0.77-10.77)	
≥16	25	3.51 (0.99-12.36)	5.60 (1.39-22.50)
APACHE II score	49	1.21 (1.12-1.31)	1.24 (1.13-1.36)

Wu et al. Scientific reports 2016

Beijing, China, Two hospitals, 2010-2014

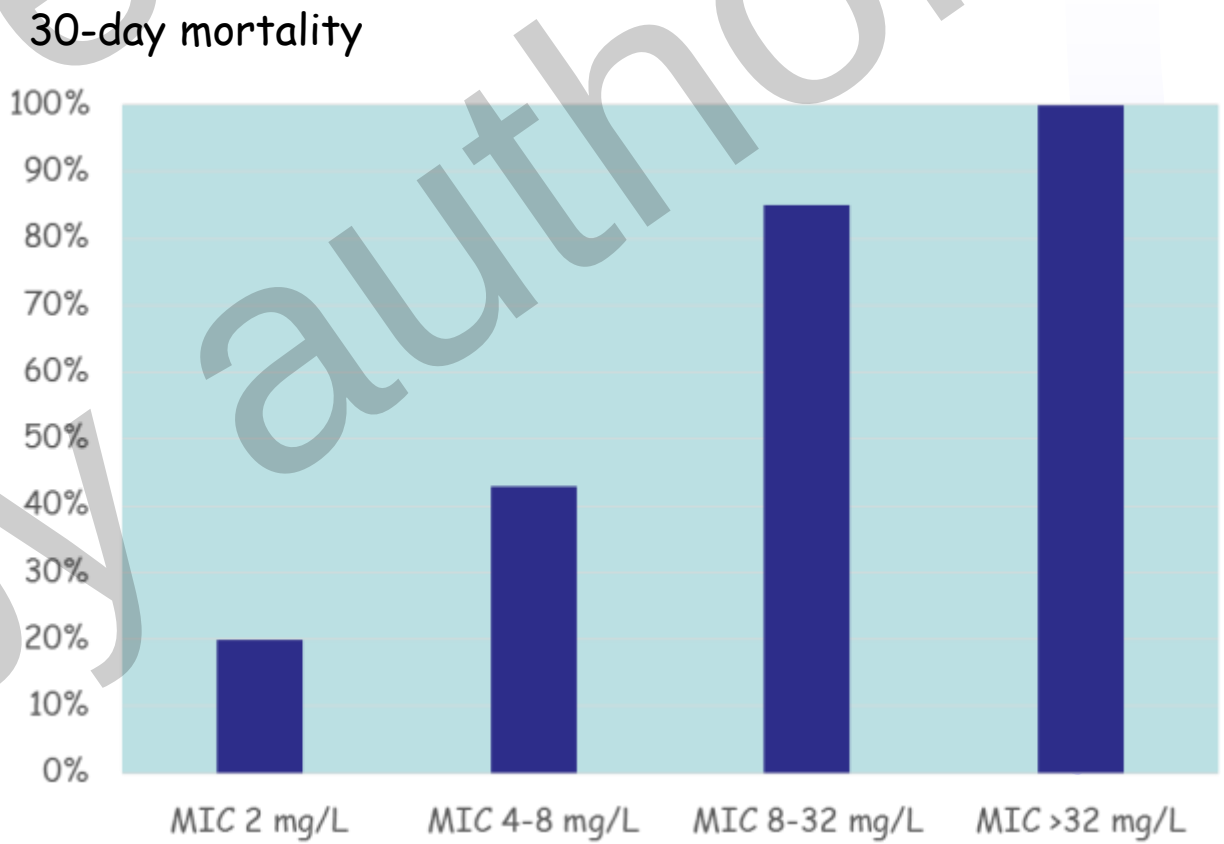
- Included patients with hospital-acquired enterobacteraceae infections
- 30-day survival in 113 patients treated with a carbapenem alone or in combination for CRE or CSE infection



Wang et al. Eur J Clin Microbiol Infect Dis 2016

Vellore, India, single center, 2014-2015

- Included children <17 years with *K. pneumoniae* or *E. coli* bacteremia, meropenem MIC ≥2 mg/L
- Mostly NDM carbapenemase
- 30-day mortality was 26/50 (52%), 7 died before receiving covering ABX
- Of 33 alive when susceptibilities were reported, 27 (82%) received meropenem, all in combination with colistin or other



Nabarro et al. Pediatr Infect Dis J 2016 EPUB

Clinical data to support carbapenem BPs

- Larger studies allowing adjustment for confounders
  - Empirical antibiotic treatment
- Monomicrobial infections where the pathogen causing the infection is certain (bacteremia only?)
- A single pathogen/ group of pathogens
- Treatment with carbapenem monotherapy, preferable clear dosing scheme
  - Minimal treatment duration
- Assessment of mortality (14/ 28 days?)

Combination therapy for carbapenemase-producing *K. pneumoniae* - Italy

- Retrospective cohort study
- Multicenter, Italy, 2010-2011
- Included adults with monomicrobial KPC-producing *K. pneumoniae* bacteremia
- Examined 30-day all-cause mortality and its relation to treatment regimen

Tumbarello et al. Clin Infect Dis 2012

Treatment and mortality

Variable	No. (%) of Patients		*P* Value	OR (95% CI)
	Nonsurvivors (n = 52)	Survivors (n = 73)		
Postantibiogram antimicrobial regimens				
Monotherapy	25 (48.1)	21 (28.7)	.02	1.59 (1.06–2.38)
Tigecycline	10 (19.2)	9 (12.3)	.28	1.32 (.81–2.16)
Colistin	11 (21.5)	11 (15.1)	.37	1.25 (.77–2.03)
Gentamicin	4 (7.6)	1 (1.3)	.09	1.98 (1.21–3.23)
Combination therapy	27 (51.9)	52 (71.2)	.02	0.62 (.41–.94)
2-drug combinations	23 (44.2)	33 (45.2)	.91	0.97 (.64–1.48)
Tigecycline + colistin	7 (13.4)	16 (21.9)	.22	0.68 (.35–1.32)
Tigecycline + gentamicin	6 (11.5)	6 (8.2)	.53	1.22 (.66–2.25)
Other 2-drug combinations[e]	10 (19.2)	11 (15.1)	.54	1.17 (.71–1.95)
3-drug combinations	4 (7.7)	19 (26.1)	.009	0.36 (.15–.92)
Tigecycline + colistin + meropenem	2 (3.8)	14 (19.2)	.009	0.27 (.07–1.01)
Other 3-drug combinations[f]	2 (3.8)	5 (6.8)	.47	0.67 (.21–2.21)
Inadequate initial antimicrobial treatment	39 (75)	36 (49.3)	.003	2.00 (1.19–3.34)

Combination therapy including meropenem

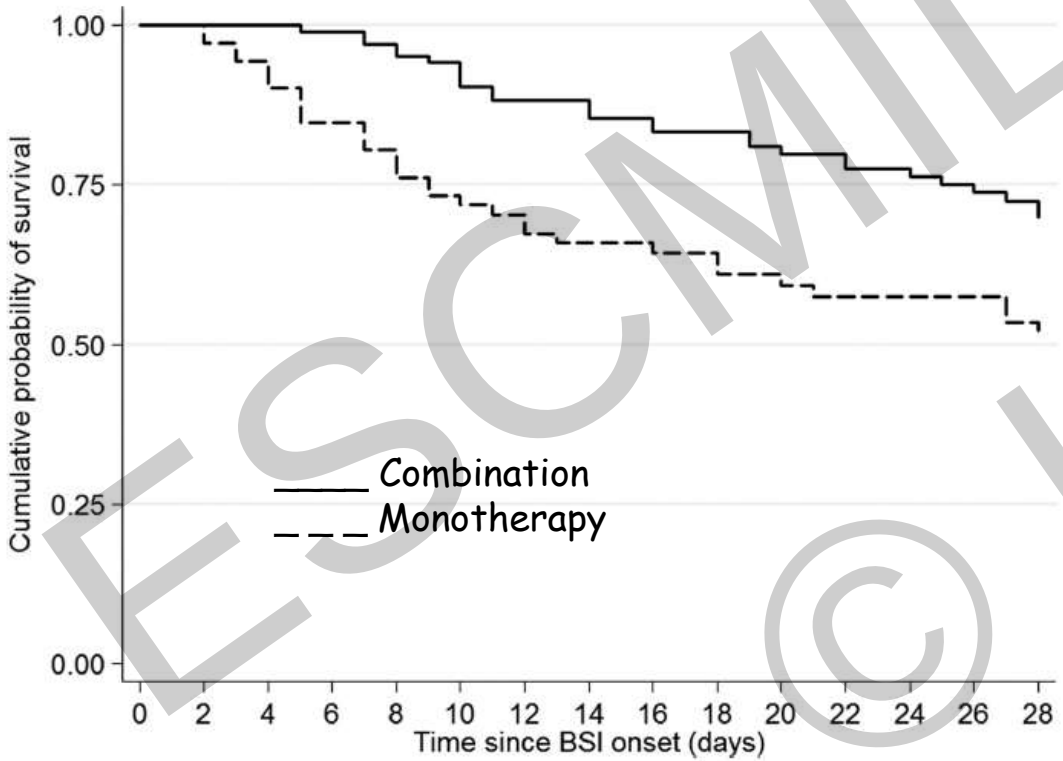
Meropenem MIC (mg/L)	Total	Non-survivors	Survivors
1	1	0	1 (100%)
2	4	0	4 (100%)
4	10	2 (20%)	8 (80%)
8	4	1 (25%)	3 (75%)
≥16	17	6 (35.2%)	11 (64.7%)
Total	36	9 (25%)	25 (75%)

Combination therapy for carbapenemase-producing *K. pneumoniae* - Greece

- Retrospective cohort study
- Two hospitals, Athens, 2009-2010
- Included adults with carbapenemase-producing *K. pneumoniae* bacteremia
- Polymicrobial bacteremias included
- Examined 28-day all-cause mortality and its relation to treatment regimen

Daikos et al. Antimicrob Agents Chemother 2014

Treatment regimen and mortality



Antimicrobial regimen	No. of patients			Mortality, %
	Total	Survived	Died	
Combination therapy	103	75	28	27.2
Carbapenem-containing regimen	31	25	6	19.3
Carbapenem + tigecycline + aminoglycoside or colistin		11	0	
Carbapenem + tigecycline		2	2	
Carbapenem + aminoglycoside		8	1	
Carbapenem + colistin		4	3	
Carbapenem-sparing regimen	72	50	22	30.6
Tigecycline + aminoglycoside + colistin		8	3	
Tigecycline + aminoglycoside		11	9	
Tigecycline + colistin		16	5	
Aminoglycoside + colistin		12	5	
Other		3	0	
Monotherapy	72	40	32	44.4
Tigecycline		16	11	
Colistin		10	12	
Aminoglycoside		7	2	
Carbapenem		5	7	
Other		2	0	
No active agent	12[a]	8	4	33.3

[a] Eight patients were infected with panresistant *Klebsiella pneumoniae*.

Combination therapy including meropenem

Carbapenem in combination with an in-vitro active drug

Carbapenem MIC (mg/L)	N patients	Deaths (%)
≤8	31	6 (19.3%)
>8	31	11 (35.5%)
All	62	17 (27.4%)

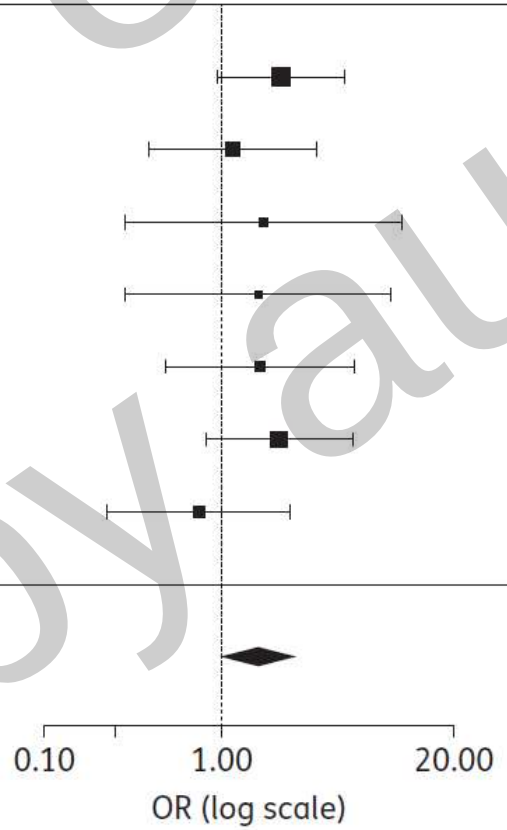
Carbapenem in combination with an in-vitro inactive drug

Carbapenem MIC (mg/L)	N patients	Deaths (%)
≤8	12	7 (58.3%)
>8	6	2 (33.3%)
All	18	9 (50%)

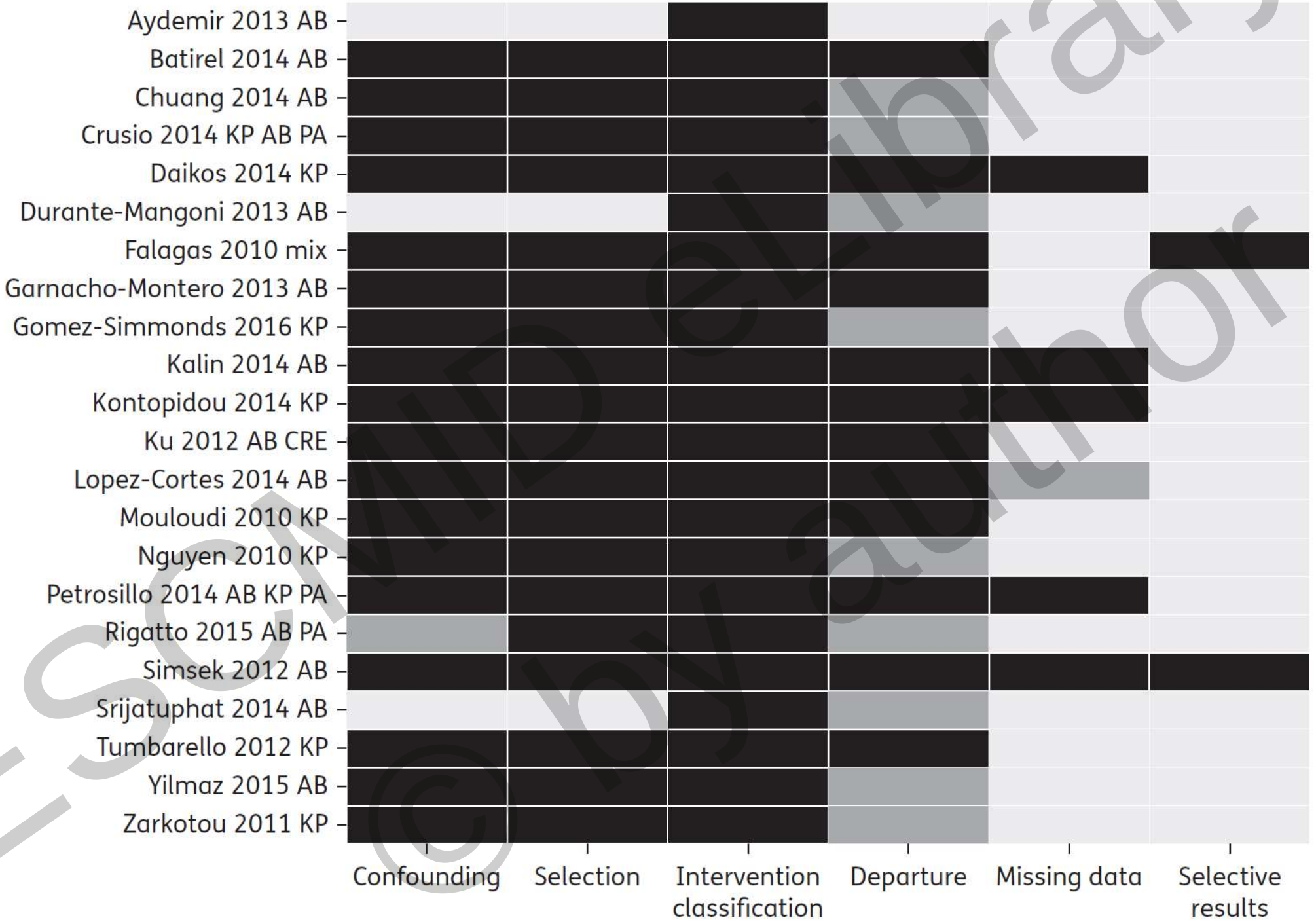
Systematic review: carabapen-polymyxin vs. polymyxin therapy for CR/CP Gram-negative infections

Author, year	Bacteria	Infection	Mono events/total	Comb events/total	Weight	OR (95% CI)
Batirel, 2014	mix	mix	26/71	7/19	26.78%	2.14 (0.93, 4.88)
Chuang, 2014	mix	mix	17/61	4/12	15.57%	1.14 (0.39, 3.38)
Crusio, 2014	KP	BSI	11/22	7/23	5.74%	1.70 (0.29, 10.17)
Daikos, 2014	KP	BSI	12/22	5/21	6.22%	1.60 (0.29, 8.90)
Petrosillo, 2014	KP	BSI	6/26	4/9	12.21%	1.64 (0.48, 5.59)
Rigatto, 2015	AB	mix	12/46	2/9	20.39%	2.09 (0.81, 5.39)
Yilmaz, 2015	KP	BSI	4/9	4/13	13.09%	0.74 (0.23, 2.43)
RE model					100.00%	1.58 (1.03, 2.42)

Heterogeneity: $\tau^2 = 0$; $\chi^2 = 2.76$, df = 6 ($P = 0.84$); $I^2 = 0$



Zusman et al. J Antimicrob Chemother 2017



Appropriate carbapenem therapy for enterobacteriaceae?

1

2

4

8

16

Significance of breakpoint change is local

Meropenem	FDA	CLSI 2010	CLSI 2013	EUCAST 2016
S	≤4	≤4	≤1	≤2
I	8	8	2	4-8
R	≥16	≥16	≥4	≥16

Susceptible definitions (S)	Italy 2010-2011, 3 hospitals, KPC-Kp BSI	Rambam 2009-2017, all Kp BSI	Rambam 2009-2017, Kp BSI MIC>1
CLSI 2010	30/125 (24%)	581/670 (86.7%)	6/95 (6.3%)
CLSI 2013	1/125 (0.8%)	575/670 (85.8%)	0/ 95 (0%)

Tumbarello et al. Clin Infect Dis 2012 and local data

Local solution: *Klebiella pneumoniae*

Antibiotic	Susceptibility	Antibiotic	Susceptibility
Amikacin	<=2.0 S	Gentamicin	>=16.0 R
Amoxicillin/CA	>=32.0 R	Colistin	<=0.5 S
Ampicillin	>=32.0 R	Ertapenem	8
Cefazolin	>=64.0 R	Imipenem	8
Ceftazidime	>=64.0 R	Meropenem	8
Ceftriaxone	>=64.0 R	Piperacillin/tazobactam	>=128.0 R
Chloramphenicol	>=64.0 R	Trimethoprim/Sulfa	>=320.0 R
Ciprofloxacin	>=4.0 R	Tigecycline	4.0 I

Thank you