III° Congresso Triveneto di Malattie Infettive
Venezia Mestre, 31 Ottobre 2015
Presidente: Prof. Enzo Raise

Infezioni invasive da Enterobacteriaceae Carbapenemico-Resistenti (CRE): da colonizzato a sepsi, quali fattori di rischio ?

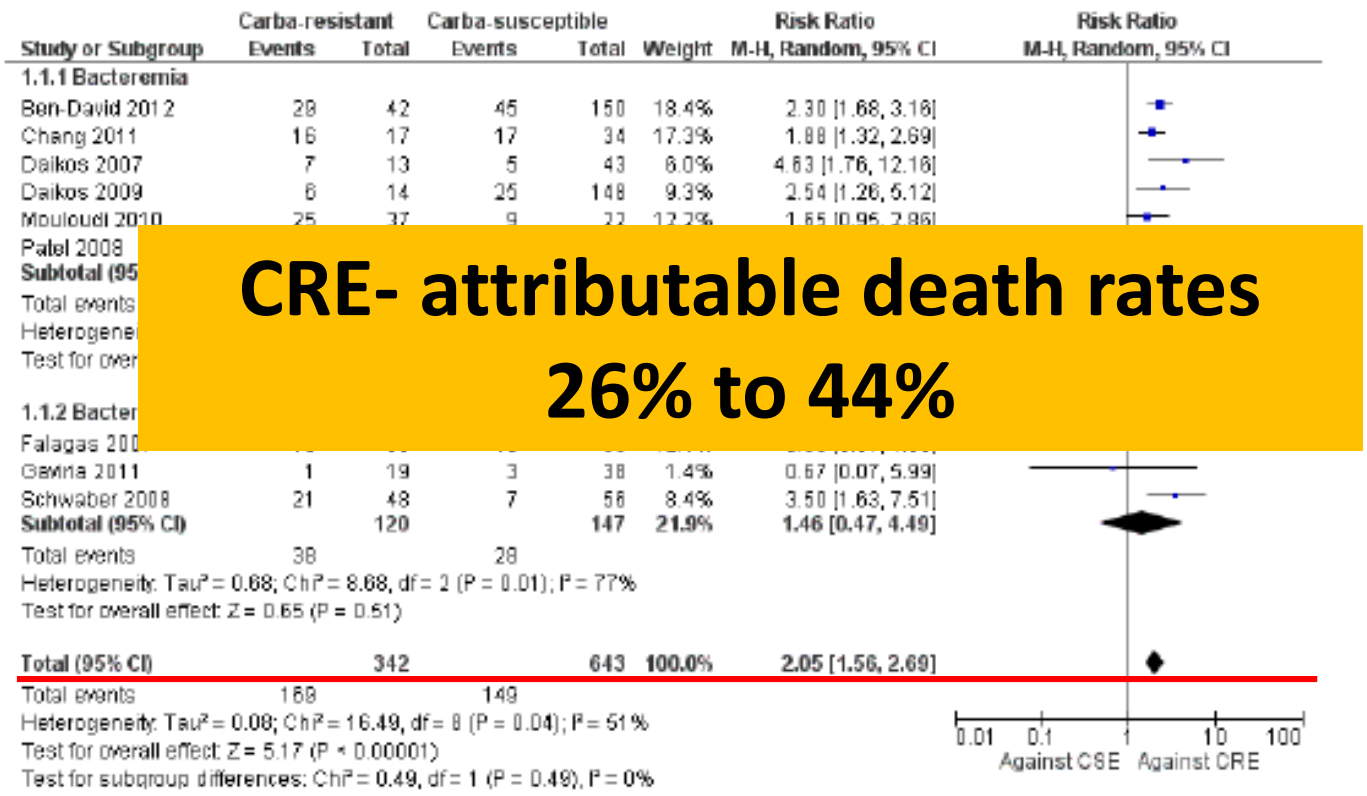
Roberto Luzzati

Malattie Infettive,

Ospedale Universitario, Trieste

Deaths Attributable to Carbapenem-Resistant *Enterobacteriaceae* Infections

Matthew E. Falagas,[1] Giannoula S. Tansarli,[1] Drosos E. Karageorgopoulos,[1] and Konstantinos Z. Vardakas[1]



CRE- attributable death rates 26% to 44%

Technical Appendix Figure. Death risk ratios (RRs) for patients infected with carbapenem-resistant Enterobacteriaceae (CRE) versus carbapenem-susceptible *Enterobacteriaceae* (CSE). Vertical line represents the point of no difference between carbapenem-resistant and carbapenem-susceptible pathogens; squares represent RRs; diamonds represent pooled RRs for all studies; horizontal lines represent 95% CIs.

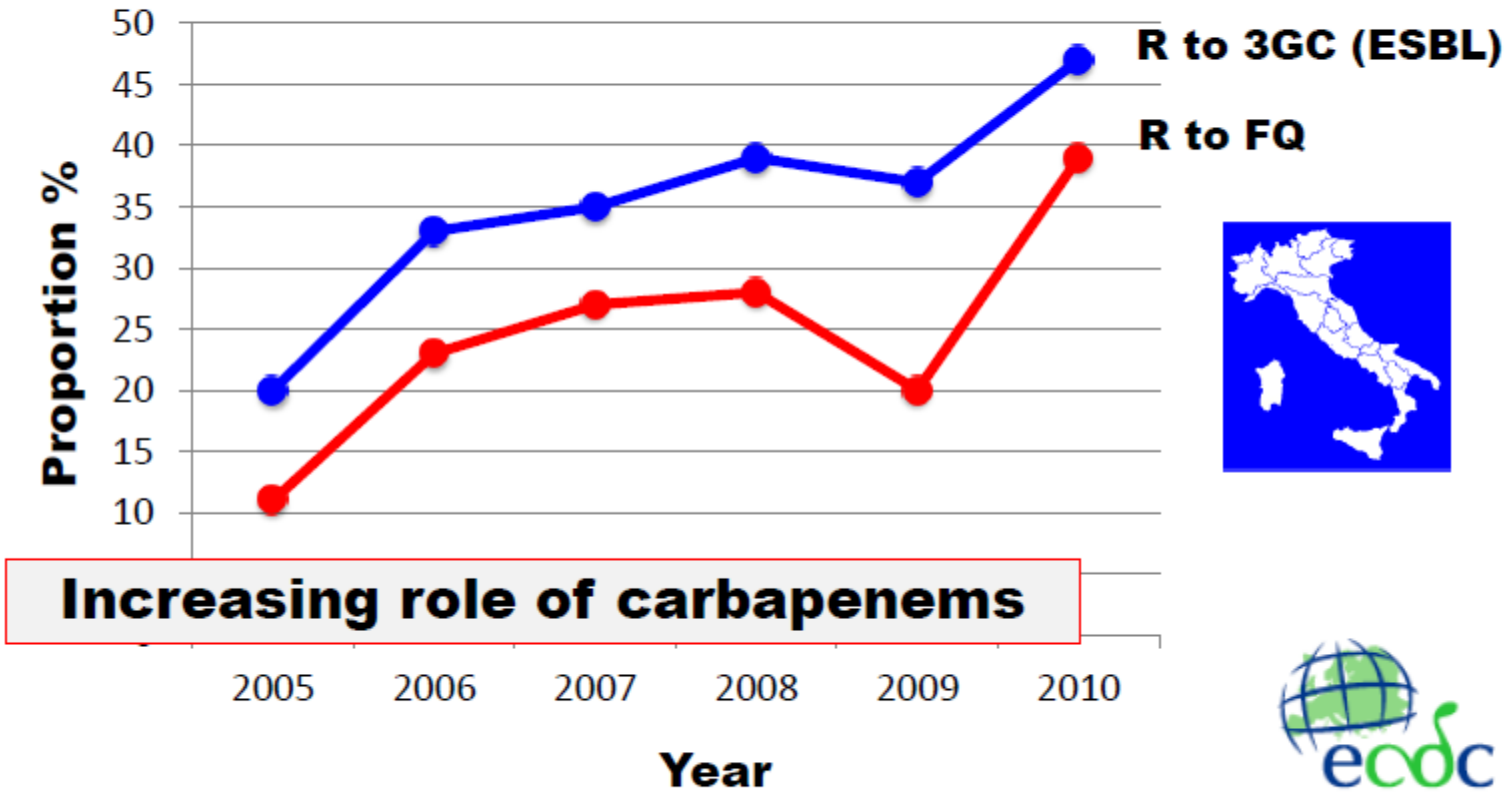
Emerg Infect Dis 2014

Identification of risk factors for infection with CRE

- … may help in the empirical therapeuthic decision-making process

- … may assist in the early implementation of appropiate infection control measures

Klebsiella pneumoniae: resistance to 3rd gen. cephalosporins and fluoroquinolones, Italy



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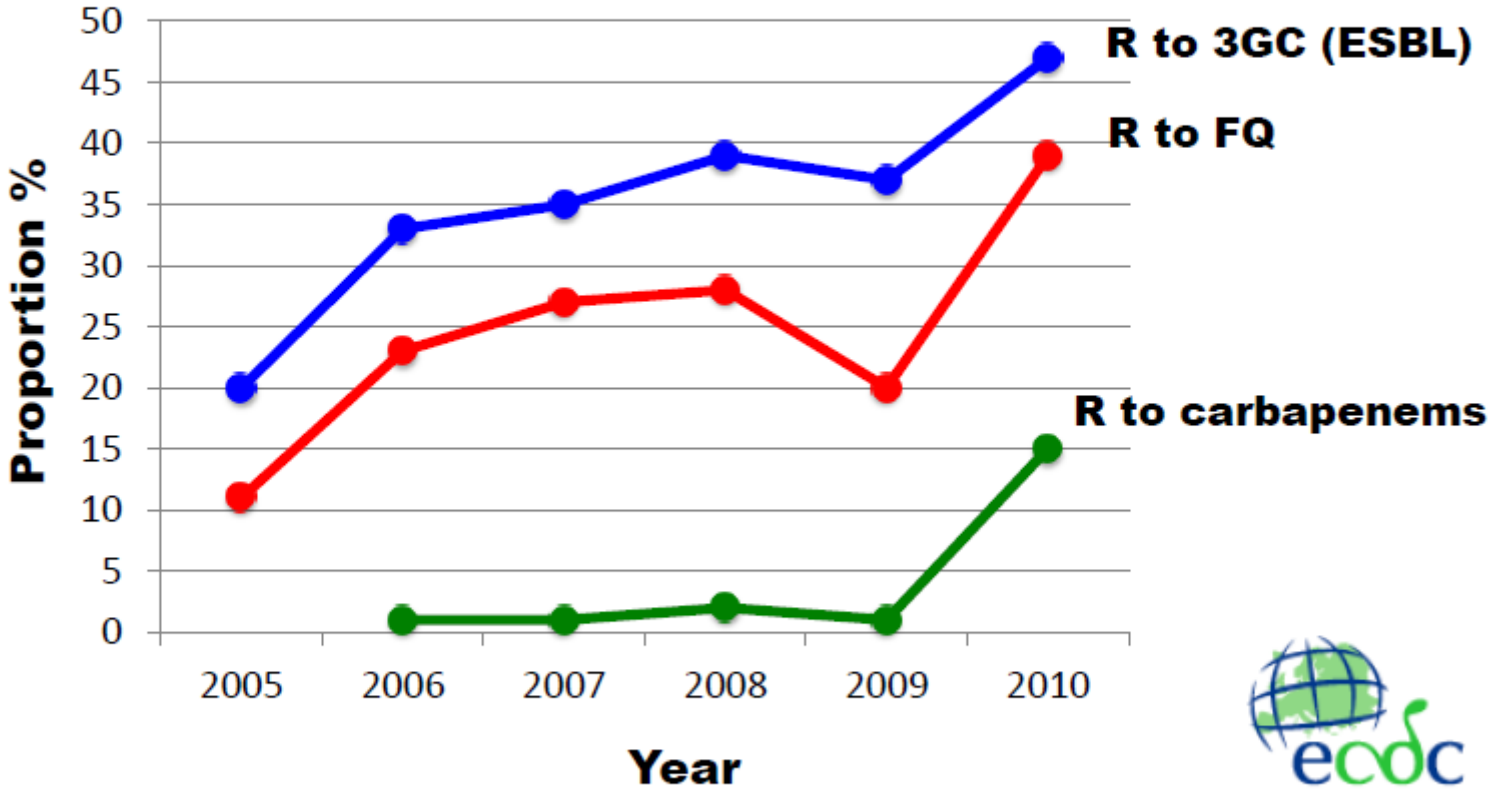
Klebsiella pneumoniae, Italy



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Predictive Models for Identification of Hospitalized Patients Harboring KPC-Producing *Klebsiella pneumoniae*

Mario Tumbarello,[a] Enrico Maria Trecarichi,[a] Fabio Tumietto,[b] Valerio Del Bono,[c] Francesco Giuseppe De Rosa,[d] Matteo Bassetti,[e] Angela Raffaella Losito,[a] Sara Tedeschi,[b] Carolina Saffioti,[c] Silvia Corcione,[d] Maddalena Giannella,[b] Francesca Raffaelli,[a] Nicole Pagani,[d] Michele Bartoletti,[b] Teresa Spanu,[f] Anna Marchese,[g] Roberto Cauda,[a] Claudio Viscoli,[c] Pierluigi Viale[b]

The production of *Klebsiella pneumoniae* carbapenemases (KPCs) by *Enterobacteriaceae* has become a significant problem in recent years. To identify factors that could predict isolation of KPC-producing *K. pneumoniae* (KPCKP) in clinical samples from hospitalized patients, we conducted a retrospective, matched (1:2) case-control study in five large Italian hospitals. The case cohort consisted of adult inpatients whose hospital stay included at least one documented isolation of a KPCKP strain from a clinical specimen. For each case enrolled, we randomly selected two matched controls with no KPCKP-positive cultures of any type during their hospitalization. Matching involved hospital, ward, and month/year of admission, as well as time at risk for KPCKP isolation. A subgroup analysis was also carried out to identify risk factors specifically associated with true KPCKP infection. During the study period, KPCKP was isolated from clinical samples of 657 patients; 426 of these cases appeared to be true infec-

AAC, 2014

TABLE 2 Logistic regression analysis of risk factors for KPCKP strain isolation and for KPCKP infection

Variable[a]	OR (95% CI)	*P*
KPCKP isolation		
≥2 previous acute-care hospitalizations[b]	5.92 (4.40–7.98)	<0.001
Indwelling central venous catheter[c]	1.66 (1.29–2.12)	<0.001
Recent carbapenem therapy[d]	2.98 (2.19–4.05)	<0.001
Recent fluoroquinolone therapy[d]	1.69 (1.29–2.21)	<0.001
Previous intensive care unit admission[b]	5.13 (3.49–7.53)	<0.001
Indwelling urinary catheter[c]	3.89 (3.03–4.99)	<0.001
Hematological cancer	1.90 (1.27–2.83)	0.002
Surgical drain[c]	1.62 (1.16–2.45)	0.004
KPCKP infection		
≥2 previous acute-care hospitalizations[b]	4.26 (3.02–6.01)	<0.001
Indwelling central venous catheter[c]	2.59 (1.91–3.50)	<0.001
Recent carbapenem therapy[d]	3.59 (2.46–5.23)	<0.001
Recent fluoroquinolone therapy[d]	2.22 (1.59–3.10)	<0.001
Charlson score ≥3[c]	7.49 (5.46–10.27)	<0.001
Recent surgical procedures[d]	2.03 (1.48–2.76)	<0.001
Neutropenia[c]	3.19 (1.50–6.78)	0.003

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CHALLENGING CLINICAL CASE IN ANTIMICROBIAL RESISTANCE

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Jose F. Camargo,[a] Jacques Simkins,[a] Thiago Beduschi,[b] Akin Tekin,[b] Laura Aragon,[c] Armando Pérez-Cardona,[d] Clara E. Prado,[e] Michele I. Morris,[a] Lilian M. Abbo[a]

Rafael Cantón (Commentator)[f,g]

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This Journal section presents a real, challenging case involving a multidrug-resistant organism. The case authors present the rationale for their therapeutic strategy and discuss the impact of mechanisms of resistance on clinical outcome. An expert clinician then provides a commentary on the case.

New antibiotic options are urgently needed for the treatment of carbapenem-resistant *Enterobacteriaceae* infections. We report a 64-year-old female with prolonged hospitalization following an intestinal transplant who developed refractory bacteremia due to a serine carbapenemase-producing pandrug-resistant isolate of *Klebsiella pneumoniae*. After failing multiple antimicrobial regimens, the patient was successfully treated.

AAC, Oct 2015

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Clinical / Microbiology

- (12 d) Abdominal abscess: KPC –S tigecy and colistin –R aminogly
- (36 d) VAT/VAP: KPC-S colistin –R tigecy and amino
- (65 d) BSI: KPC – S colistin -R tigecy, aminogly and fosfomycin
- ……

Therapy/Outcome

- Tigecy + colistin: **CURE** (renal insuff iciency)
- Meropenem + colistin: **CURE**
- …..
- …..

J Antimicrob Chemother 2015; **70**: 2133–2143
doi:10.1093/jac/dkv086 Advance Access publication 21 April 2015

Journal of Antimicrobial Chemotherapy

Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

Mario Tumbarello[1]*, Enrico Maria Trecarichi[1], Francesco Giuseppe De Rosa[2,3], Maddalena Giannella[4], Daniele Roberto Giacobbe[5], Matteo Bassetti[6], Angela Raffaella Losito[1], Michele Bartoletti[4], Valerio Del Bono[5], Silvia Corcione[2,3], Giuseppe Maiuro[1], Sara Tedeschi[4], Luigi Celani[1], Chiara Simona Cardellino[2,3], Teresa Spanu[7], Anna Marchese[8], Simone Ambretti[9], Roberto Cauda[1], Claudio Viscoli[5] and Pierluigi Viale[4] on behalf of ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)

Objectives: Infections caused by *Klebsiella pneumoniae* (Kp) carbapenemase (KPC)-producing strains of Kp have become a significant threat in recent years. To assess their outcomes and identify risk factors for 14 day mortality, we conducted a 4 year (2010–13) retrospective cohort study in five large Italian teaching hospitals.

Methods: The cohort included 661 adults with bloodstream infections (BSIs; $n=447$) or non-bacteraemic infections (lower respiratory tract, intra-abdominal structure, urinary tract or other sites) caused by a KPC-Kp isolate. All had received ≥48 h of therapy (empirical and/or non-empirical) with at least one drug to which the isolate was susceptible.

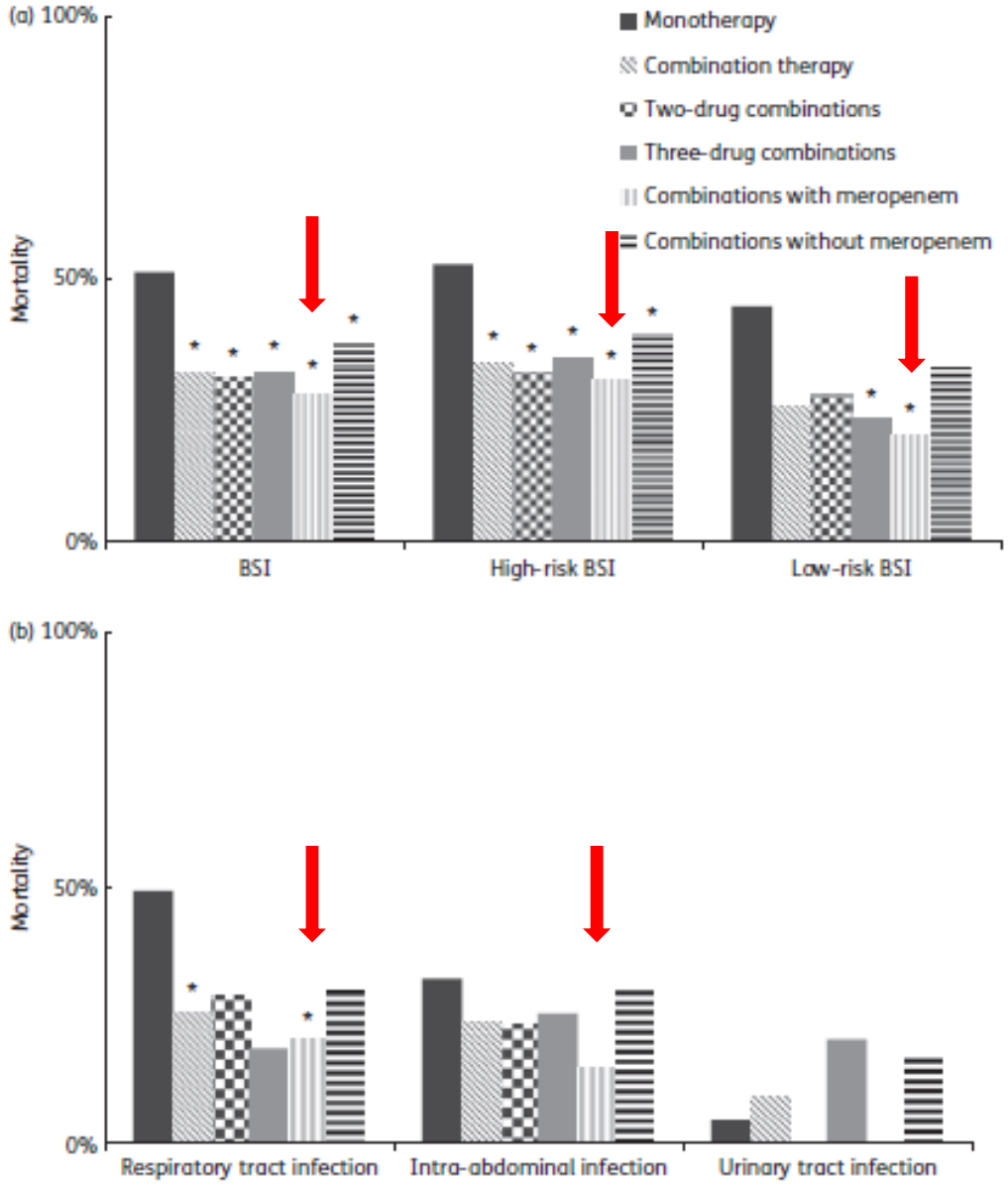

Figure 2. Mortality rates associated with different antimicrobial drug regimen categories in patients with BSIs (a) or non-bacteraemic infections (b). *Statistically significant differences ($P<0.05$) among different types of combination therapy and monotherapy.

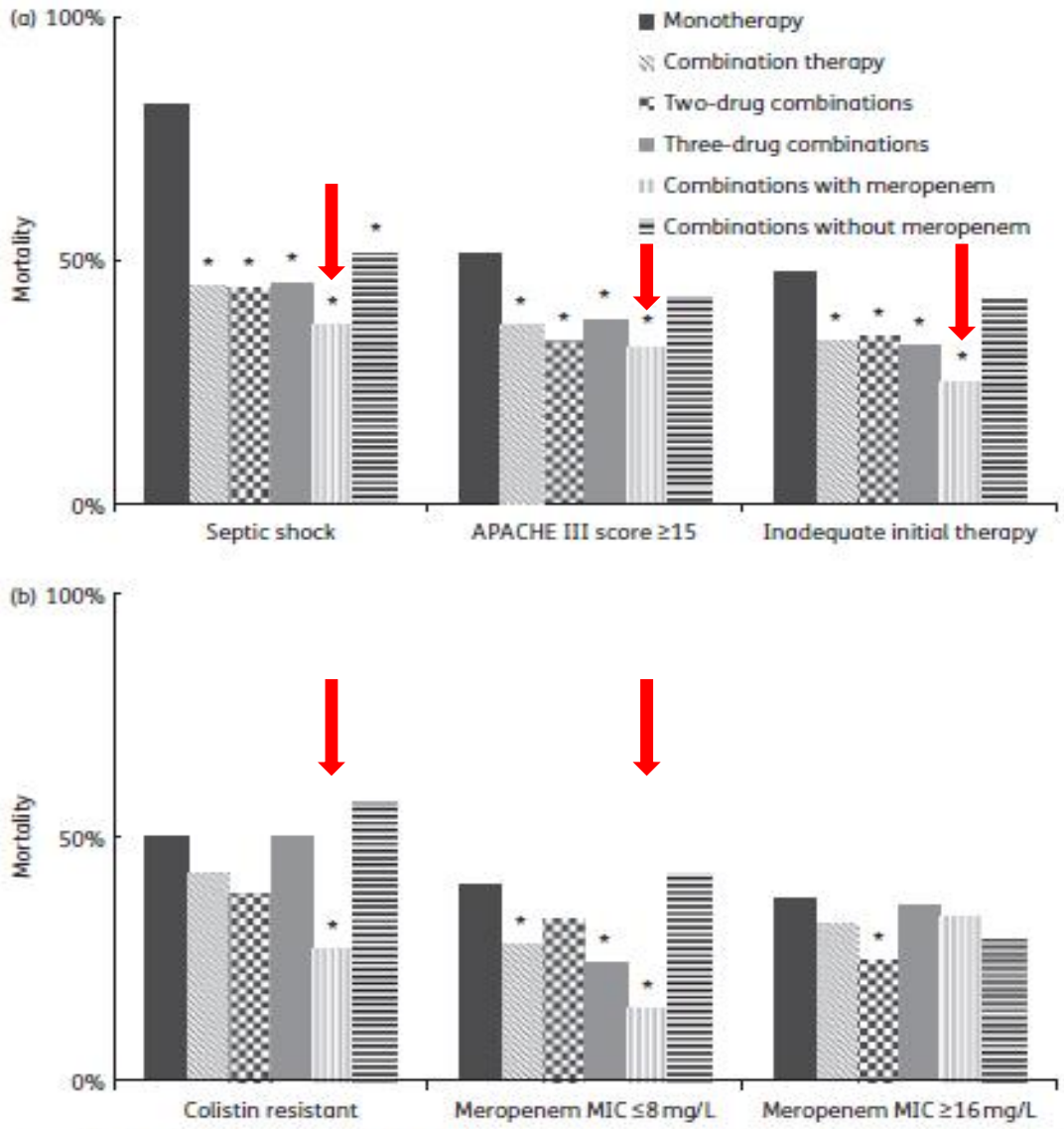

Figure 3. Mortality rates associated with different antimicrobial drug regimen categories in patients with different presenting features (a) or in patients with different KPC-Kp isolate characteristics (b). *Statistically significant differences ($P < 0.05$) among different types of combination therapy and monotherapy.

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Clinical / Microbiology

- (12 d) Abdominal abscess: KPC –S tigecy and colistin –R aminogly
- (36 d) VAT/VAP: KPC-S colistin –R tigecy and amino
- **(65 d) BSI: KPC – S colistin -R tigecy, aminog and fosfomycin**
- **(72 d) BSI: KPC –R colistin (MIC, 12 ug/ml)**

Therapy/Outcome

- Tigecy + colistin: CURE, renal failure
- Merop + colistin: CURE
- **Merop + colistin + tigecy: FAILURE (persistent BSI-KPC)**

Risk factors for bloodstream infections due to colistin-resistant KPC-producing *Klebsiella pneumoniae*: results from a multicenter case–control–control study

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The increasing prevalence of colistin resistance (ColR) *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* (Kp) is a matter of concern because of its unfavourable impact on mortality of KPC-Kp bloodstream infections (BSI) and the shortage of alternative therapeutic options. A matched case–control–control analysis was conducted. The primary study end point was to assess risk factors for ColR KPC-Kp BSI. The secondary end point was to describe mortality and clinical characteristics of these infections. To assess risk factors for ColR, 142 patients with ColR KPC-Kp BSI were compared to two controls groups: 284 controls without infections caused by KPC-Kp (control group A) and 284 controls with colistin-susceptible (ColS) KPC-Kp BSI (control group B). In the first multivariate

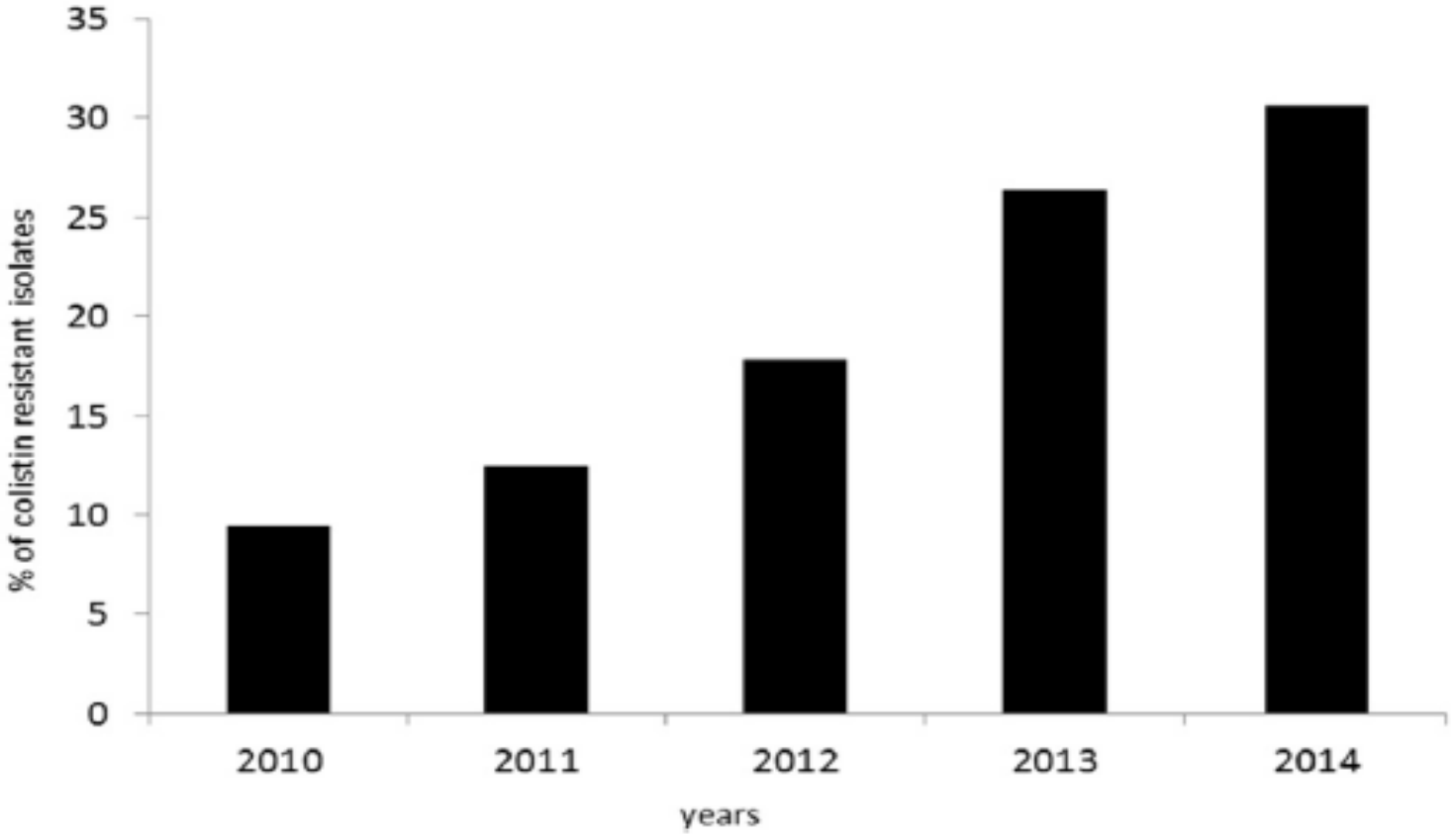

FIG. 1. Increase in colistin resistance (ColR) among blood *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* isolates during the study period (χ^2 for trend, $p < 0.001$).

TABLE 2. Multivariate analysis of risk factors for BSI caused by colistin-resistant KPC-Kp[a]

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

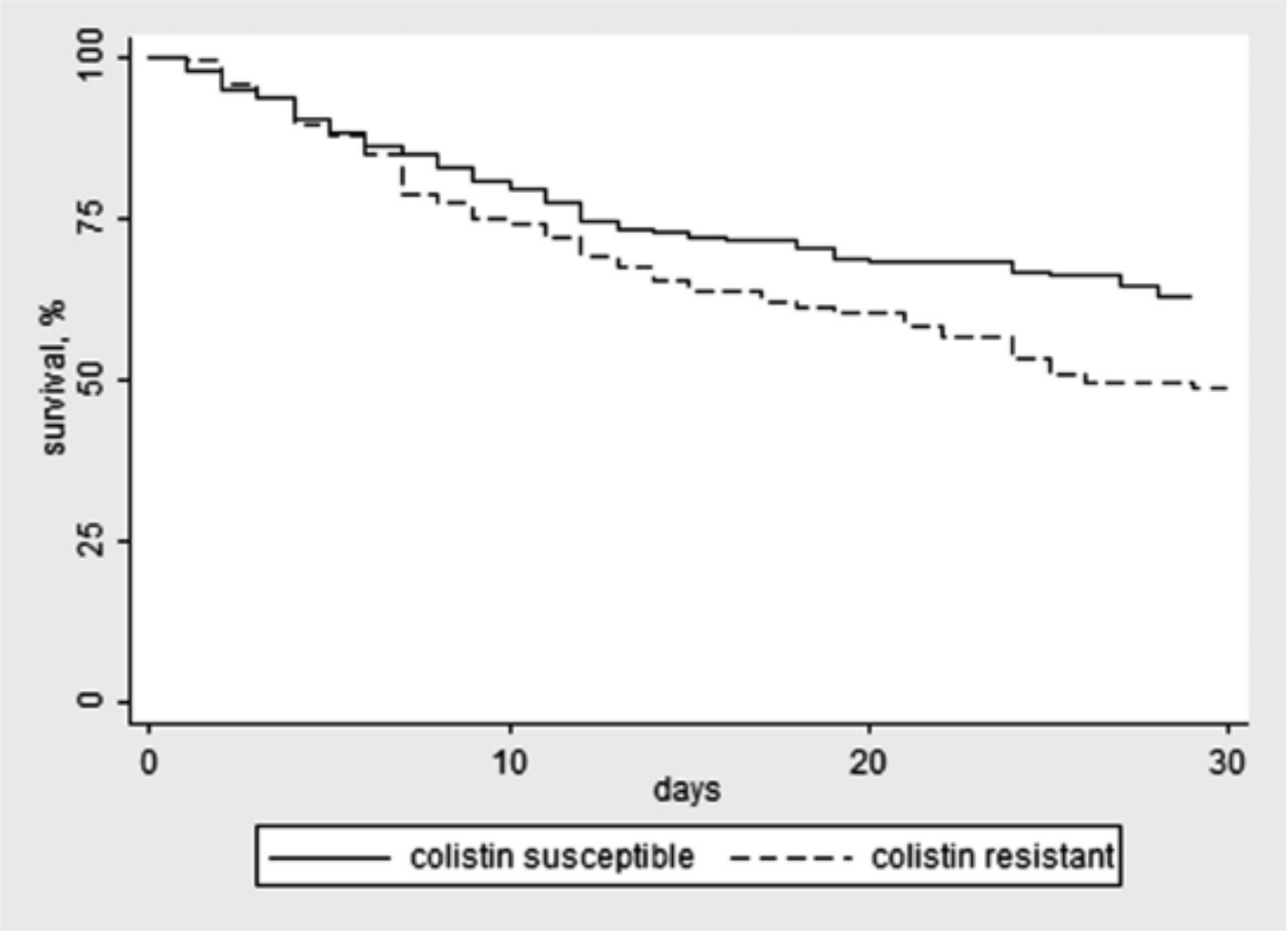

FIG. 2. Kaplan-Meier survival curves of patients with bloodstream infection due to *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* according to colistin resistance or susceptibility of isolates.

Klebsiella pneumoniae - KPC

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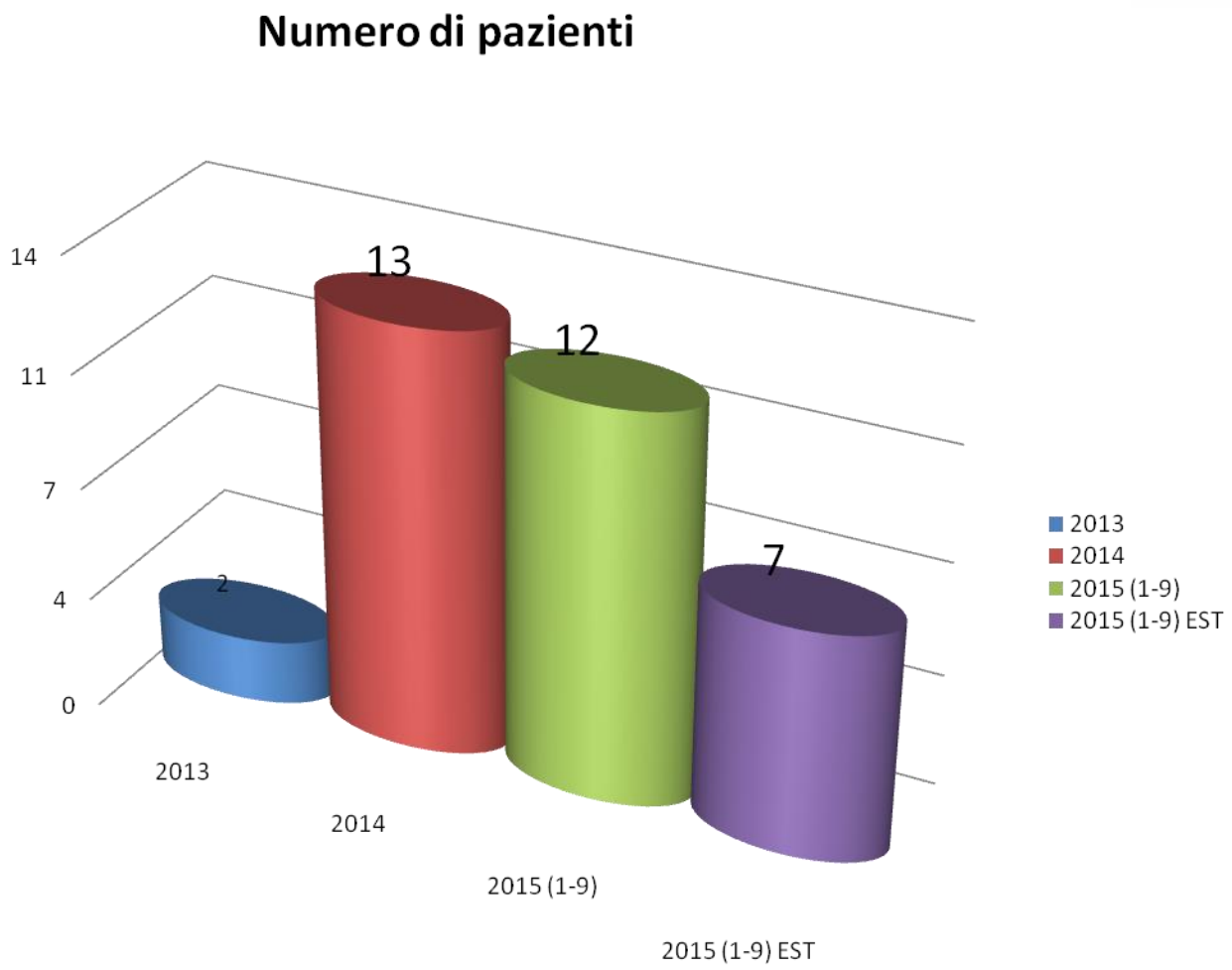

Klebsiella pneumoniae - KPC

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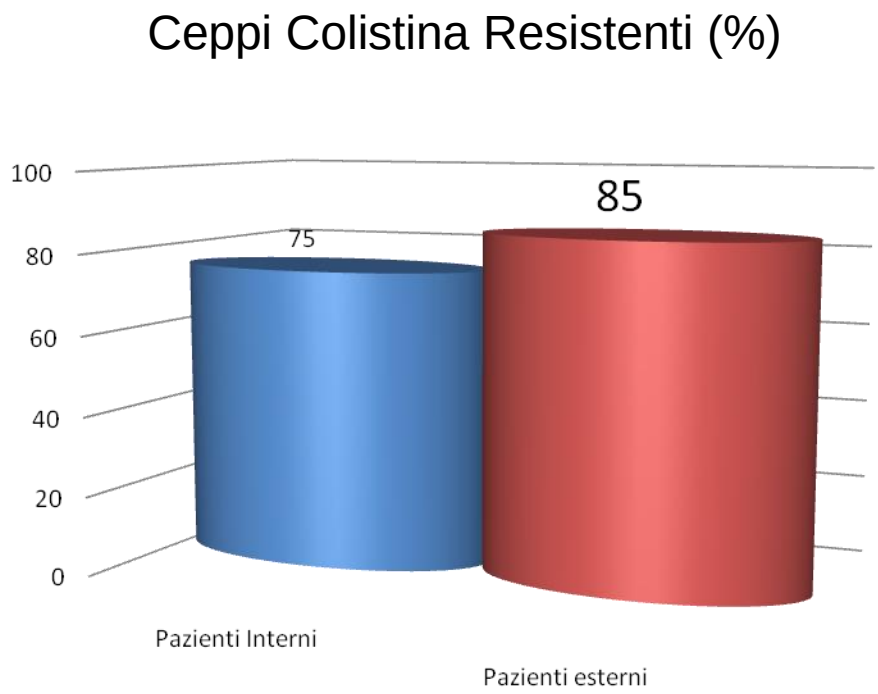

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

CHALLENGE QUESTION

Assuming that adequate source control has been achieved, the addition of which of the following therapeutic options is more appropriate for this patient?

A. Intravenous fosfomycin
B. Dual-carbapenem therapy
C. Ceftazidime-avibactam
D. Other

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Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

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6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece

Ertapenem plus doripenem or meropenem were given in three patients suffering from pandrug-resistant, KPC-2-positive *Klebsiella pneumoniae* bacteremia (2 patients) and urinary tract infection (1 patient), respectively. All responded successfully, without relapse at follow-up. The results obtained should probably be attributed to ertapenem's increased affinity for the carbapenemases hindering doripenem/meropenem degradation in the environment of the microorganism.

AAC, 2013

TABLE 2 Reported clinical cases of double-carbapenem therapy in patients infected with multidrug-resistant and pan-drug resistant *K. pneumoniae*, including carbapenemase producers[a]

Reference or source and country	Underlying disease(s)	Clinical sample(s)	Microorganism	Drugs and MICs (μg/ml)[b]	Dual-carbapenem therapy (dose and infusion conditions when included)	Treatment duration, comments, and outcome
Giamarellou et al. (11), Greece	Spinal cord injury	Blood, urine, CVC	KPC-2-producing *K. pneumoniae*	ERT, >8; MER, >32; DOR, >8; CST, >16	ERT (1 g q24h i.v.) + DOR (2 g q8h i.v., 4-h infusion, 1 h after ERT)	20-day treatment. Patient became afebrile on day 4 with negative blood and cultures after 2 days of treatment. No relapse after 10 mos of follow-up.
	Subarachnoid hemorrhage	Blood, urine	KPC-2-producing *K. pneumoniae*	ERT, >8; MER, >32; DOR, >8; CST, >16	ERT (1 g q24h i.v.) + MER (1 g q8h i.v., 3-h infusion, 1 h after ERT)	14-day treatment. MER dose reduced due to renal function. Patient became afebrile on day 3, and blood and urine cultures were sterile during therapy and after 3-wk follow-up.
	Spinal cord injury	Urine	KPC-2-producing *K. pneumoniae*	ERT, >8; MER, >32; DOR, >8; CST, >16	ERT (1 g q24h i.v.) + MER (2 g q8h i.v., 3-h infusion, 1 h after ERT)	10-day treatment. Sterile urine cultures after 2 days of treatment. No relapse after 6 mos of follow-up
Ceccarelli et al. (12), Italy	Cerebral hemorrhage	Blood, endotracheal aspirate	KPC-3-producing *K. pneumoniae*	ERT, 256–512; MER, 64; DOR, 32–64; CST, 16–31	ERT (0.5–1 g q24h i.v.) + DOR (0.25–1 g q8h i.v., 4-h infusion)	21-day treatment. Bacteremia cleared after 8-day of treatment. ERT and DOR doses were adjusted during treatment to renal clearance. No relapse 1 mo after end of treatment.
Oliva et al. (25), Italy	Aortic prosthesis replacement	Blood	Carbapenemase-producing *K. pneumoniae*	ERT, 128; MER, 256; CST, ≥16	ERT (1 g q24h i.v.) + MER (2 g q8h i.v.)	21-day treatment. Recovered after treatment.
	Left lower limb revascularization	Blood	Carbapenemase-producing *K. pneumoniae*	ERT, 256; MER, 256; CST, ≥16	ERT (0.5 g q24h i.v.) + MER (1 g q12h i.v.)	MER adjusted to renal function. Microbiological eradication after 48 h of treatment. Death due to heart failure after 4 days of treatment.
	Renal hematoma	Blood	Carbapenemase-producing *K. pneumoniae*	ERT, 256; MER, 128; CST, ≥16	ERT (1 g q24h i.v.) + MER (2 g q8h i.v.)	24-day treatment. Clinical recovery.
	Hip joint replacement	Blood, CVC	Pan-drug-resistant *K. pneumoniae*	ERT, 128; MER, 256; CST, 32	ERT (1 g q24h i.v.) + MER (2 g q8h i.v., 4-h infusion) + CST (6 MU loading dose, 4.5 MU q12h)	21-day treatment (7 days with CST). Sterile blood and urine cultures after 4 days of treatment.
Chua et al. (27), Singapore	Necrotizing pancreatitis	Sputum	KPC-producing *K. pneumoniae*	ERT, 4; MER, 16; DOR, 8; POL-B, 1	ERT (1 g q24h i.v.) + DOR (1 g q8h i.v., 4-h infusion, 2 h after ERT) + POL-B (750,000 U q12h i.v.) + CST (inhaled 2 MU q8h)	12-day treatment. Microbiological eradication after 1-day treatment. Clinical recovery but death due to heart failure 1 mo after end of treatment.
	Adenocarcinoma and hepatocarcinoma	Blood, sputum, abdominal wound	KPC-producing *K. pneumoniae*	ERT, >32; MER, >32; IMI, >32; CST (not determined)	ERT (0.5 g q24h i.v.) + DOR (0.5 g q8h i.v., 2 h after ERT) + POL-B (750,000 U q12h i.v.)	10-day treatment. Microbiological eradication in sputum and abdominal wound after 5 days of treatment. Relapse 10 days after end of treatment in blood cultures but not in sputum sample
Camargo et al. (present case article), United States	Intestinal transplant	Abdominal wound, blood, urine, CVC	KPC-producing *K. pneumoniae*	ERT R, MER R, IMI R; CST, 0.19–1; CAZ-AVI, ≤4	ERT (1 g q24h i.v.) + MER (1 g q12h, 2 h after ERT) + CST (750,000 U q12h)	12-day treatment (adjusted to renal function). Initial response but breakthrough bacteremia after 12 days of treatment. CST resistance development (MIC, 12 μg/ml).

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Clinical / Microbiology

- Abdominal abscess: KPC –S tigecy and colistin –R aminoglycoside
- VAT/VAP: KPC-S colistin –R tigecy and amino
- BSI: KPC – S colistin -R tigecy, aminog and fosfomycin
- **(72 d) BSI: KPC –R colistin (MIC, 12 ug/ml)**

Therapy/Outcome

- Tigecy + colistin: CURE + renal failure
- Merop + colistin: CURE
- Merop + colistin + tigecy: FAILURE (persistent BSI-KPC)
- **Colistin + merop + ertapenem: initial response > FAILURE**

Table 2. β-Lactamase Inhibitor Combinations.

Inhibitor	Spectrum	Combination Antibiotics
Clavulanic acid[28-30]	Class A narrow spectrum	Amoxicillin
	Class A ESBLs	Ticarcillin
Tazobactam[6,39]	Class A narrow spectrum	Piperacillin
	Class A ESBLs	Ceftolozane
	Some class C enzymes	
Sulbactam[19,35,37]	Class A narrow spectrum	Ampicillin
	Class A ESBLs	Piperacillin
		Cefoperazone
Avibactam[46-48]	Class A narrow spectrum	Ceftaroline
	Class A ESBLs	Ceftazidime
	Class A carbapenemases	Aztreonam
	Some class C and class D enzymes	
MK-7655[75,76]	Class A narrow spectrum	Imipenem
	Class A ESBLs	
	Class A carbapenemases	
	Some class C enzymes	
RPX7009[83,84,85]	Class A narrow spectrum	Biapenem
	Class A ESBLs	
	Class A carbapenemases	
	Some class C enzymes	

Abbreviation: ESBL, extended-spectrum β-lactamase.

Annals of Pharmacotherapy

Kimberly A. et al.-2015

CEFTAZIDIME-AVIBACTAM: a novel cephalosporin/betalactase inhibitor combination

- Ceftazidime is a third generation cephalosporin; resistance, especially with gram negative bacilli, is increasing globally
- Avibactam (NXL 104) is a non betalactam betalactamase inhibitor active in vitro against class A and C and some class D betalactamases
- Avibactam is being developed in combination with cefatzidime and with ceftaroline
- Ceftazidime-avibactam is currently in phase III clinical trials for treatment of UTI and IAI complicated

Successful Treatment of Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae* Bacteremia

Clinical / Microbiology

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- VAT/VAP: KPC-S colistin –R tigecy and amino
- BSI: KPC – S colistin -R tigecy, aminog and fosfomycin
- BSI: KPC –R colistin (MIC, 12 ug/ml)

Therapy/Outcome

- Tigecy + colistin: CURE + renal failure
- Merop + colistin: CURE
- Merop + colistin + tigecy: FAILURE (persistent BSI-KPC)
- Colistin + merop + ertapenem: initial response > FAILURE
- **Ceftazidime/avibactam 1000 mg /250 mg + ertapenem 1 g: CURE**

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