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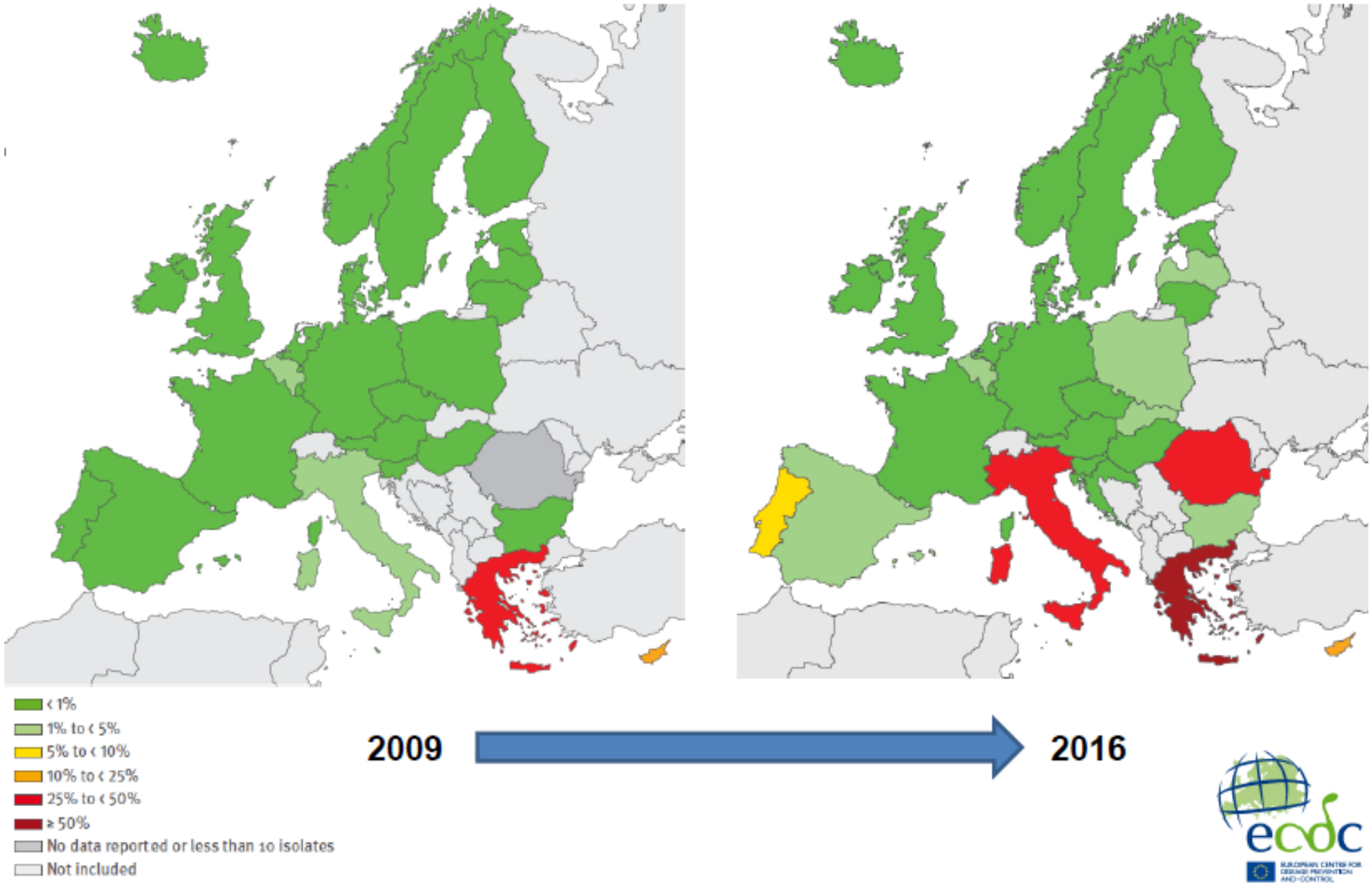
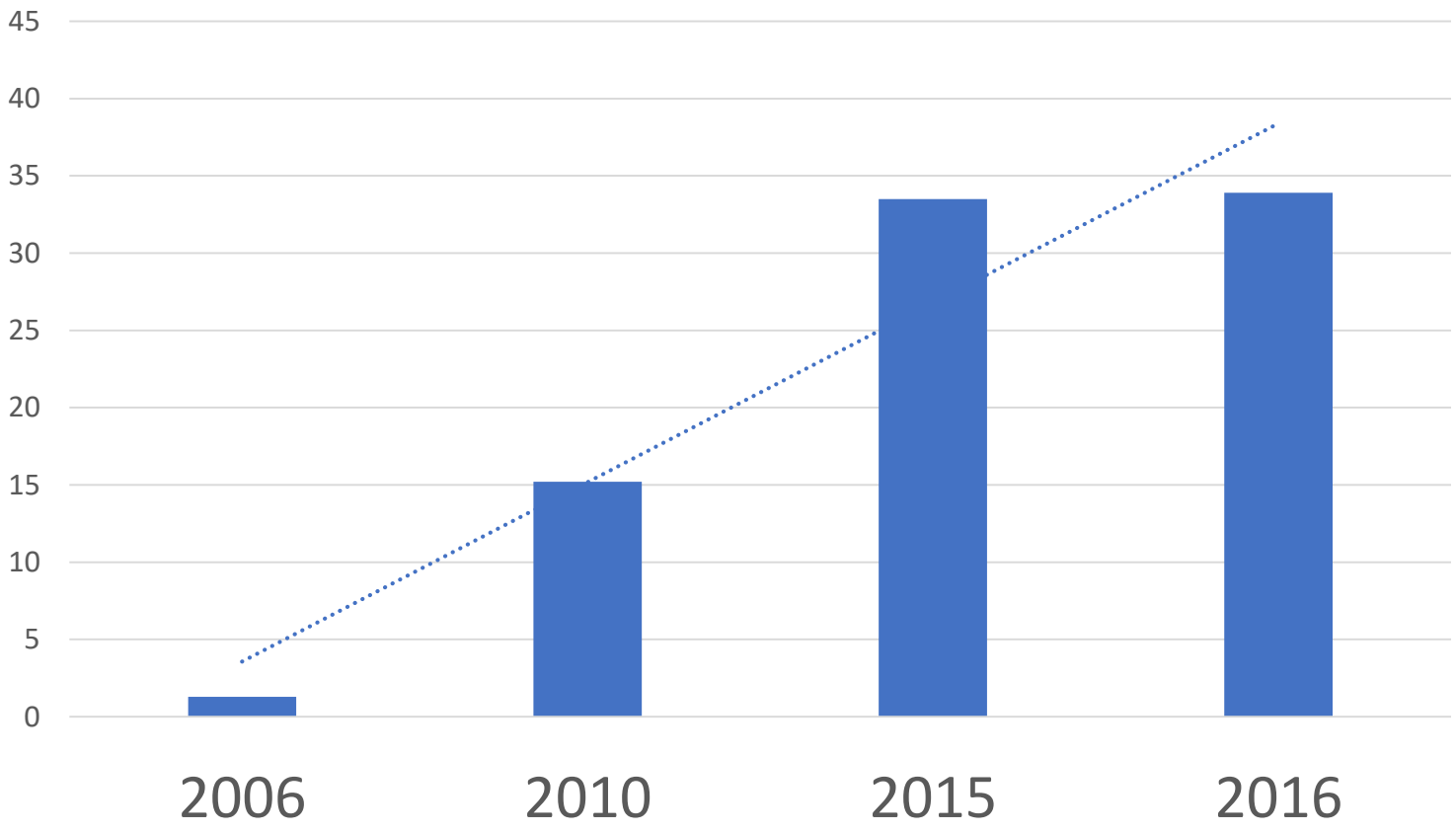
Klebsiella pneumoniae: percentage of invasive isolates with resistance to carbapenems



Tasso di resistenza ai carbapenemici tra le Klebsielle isolate, dato **Italia** ECDC



International Journal of Infectious Diseases 68 (2018) 50–53

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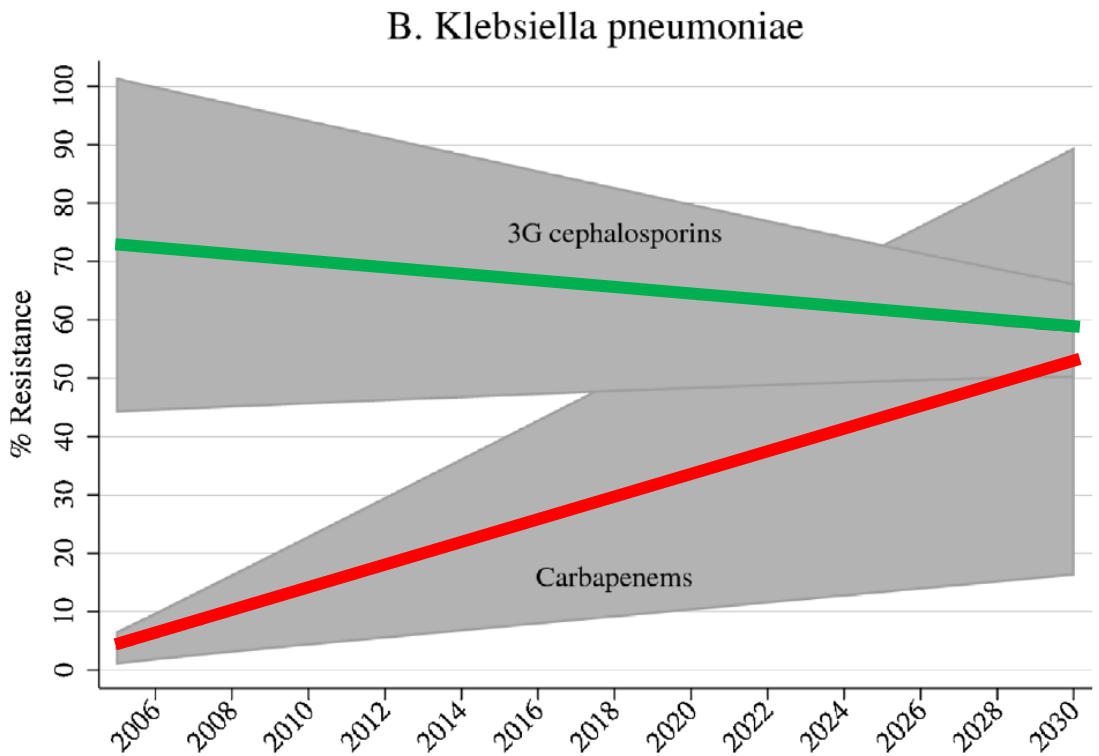
journal homepage: www.elsevier.com/locate/ijid

Short Communication

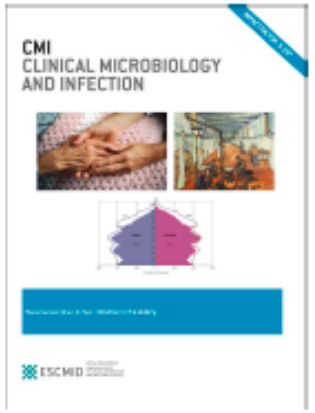
Global forecast of antimicrobial resistance in invasive isolates of *Escherichia coli* and *Klebsiella pneumoniae*

Gerardo Alvarez-Uria[a], Sumanth Gandra[b,c], Siddhartha Mandal[d], Ramanan Laxminarayan[b,c,e,*]



Carbapenem-resistant *Enterobacteriaceae* in wildlife, food-producing and companion animals – a systematic review

Robin Köck, Inka Daniels-Haardt, Karsten Becker, Alexander Mellmann, Alexander W. Friedrich, Dik Mevius, Stefan Schwarz, Annette Jurke



- Tamponi rettali degli animali da compagnia
- Tamponi rettali maiali
- Pollame
- Latte
- Carne
- Pesci ornamentali
- Seafood

Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis

Evelina Tacconelli, Elena Carrara, Alessia Savoldi*, Stephan Harbarth, Marc Mendelson, Dominique L Monnet, Céline Pulcini, Gunnar Kahlmeter, Jan Kluytmans, Yehuda Carmeli, Marc Ouellette, Kevin Outterson, Jean Patel, Marco Cavaleri, Edward M Cox, Chris R Houchens, M Lindsay Grayson, Paul Hansen, Nalini Singh, Ursula Theuretzbacher, Nicola Magrini, and the WHO Pathogens Priority List Working Group†*

Summary

Background The spread of antibiotic-resistant bacteria poses a substantial threat to morbidity and mortality worldwide. *Lancet Infect Dis* 2017

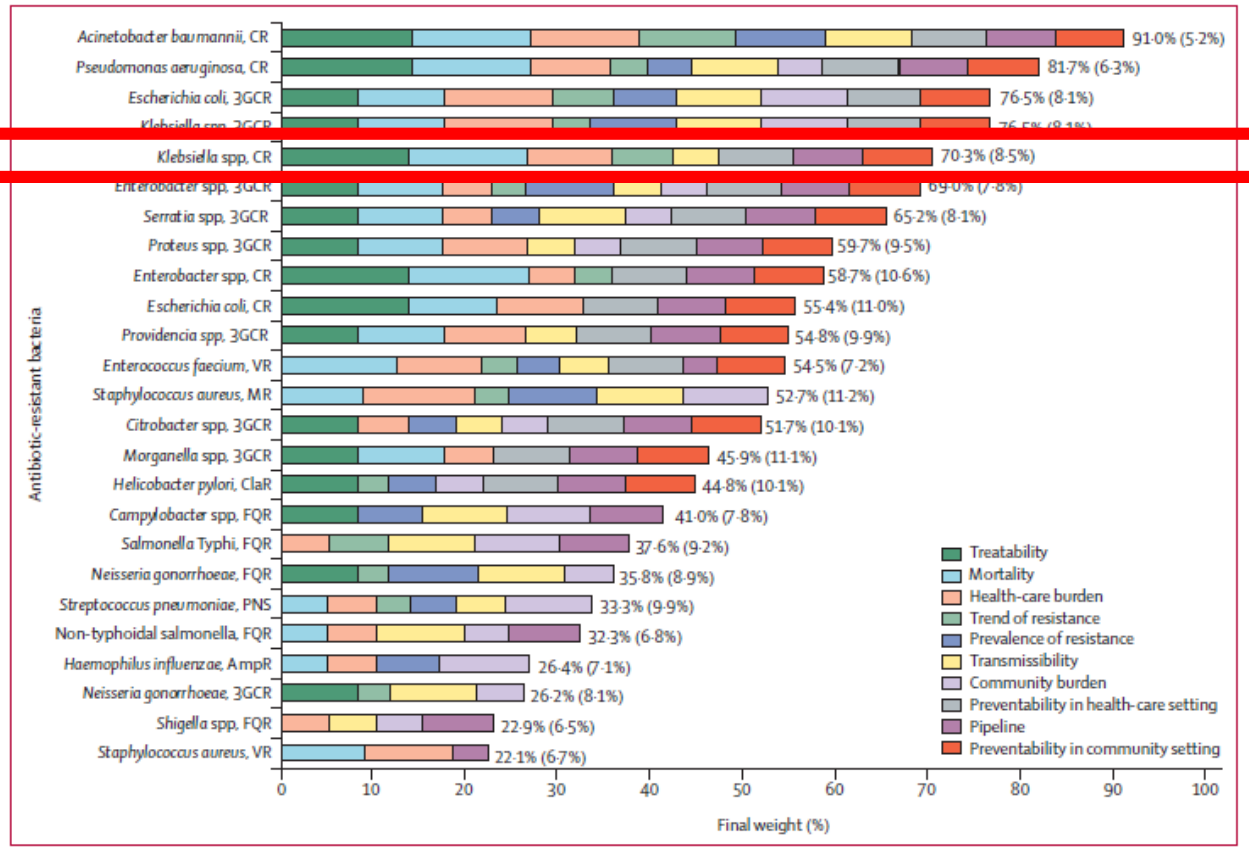


Figure 2: **Final ranking of antibiotic-resistant bacteria**
Mean (SD) pathogen weights were derived by the software from the survey participants' preferences. The segments represent the contribution of each criterion to each pathogen's final weight. CR=carbapenem resistant. 3GCR=third-generation cephalosporin resistant. VR=vancomycin resistant. MR=meticillin resistant. ClaR=clarithromycin resistant. FQR=fluoroquinolone resistant. PNS=penicillin non-susceptible. AmpR=ampicillin resistant.

Panel: WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria

Multidrug-resistant and extensively-resistant *Mycobacterium tuberculosis*[25]

Other priority bacteria

Priority 1: critical

- *Acinetobacter baumannii*, carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third-generation cephalosporin resistant

Priority 2: high

- *Enterococcus faecium*, vancomycin resistant
- *Staphylococcus aureus*, methicillin resistant, vancomycin resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter* spp, fluoroquinolone resistant
- *Salmonella* spp fluoroquinolone resistant
- *Neisseria gonorrhoeae*, third-generation cephalosporin resistant, fluoroquinolone resistant

Priority 3: medium

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin resistant
- *Shigella* spp, fluoroquinolone resistant

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Fattori di rischio per acquisizione CRE

A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant *Enterobacteriaceae*

Karlijn van Loon,[a] Anne F. Voor in 't holt,[a] Margreet C. Vos[a]

[a]Department of Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands

TABLE 3 Random-effects meta-analyses of antibiotic exposure and other risk factors and/or protective factors for acqui

Associated risk factor	No. of times identified	Pooled OR (95% CI)	*P* value for risk of publication bias by use of the indicator of:	
			Egger et al. (28)	Begg and Mazumdar (29)
Antibiotic exposure				
Carbapenem use	25	4.71 (3.54–6.26)	<0.05	<0.05
Cephalosporin use	16	4.49 (2.42–8.33)	<0.05	<0.05
Quinolone use	10	2.46 (1.44–4.23)	<0.05	0.29
Other β-lactam use	9	2.00 (1.49–2.70)	<0.05	0.26
Glycopeptide use	5	4.18 (2.30–7.60)	<0.05	<0.05
Other risk factors				
Underlying disease or condition	31	2.54 (2.08–3.09)	<0.05	0.12
Invasive procedures	20	4.67 (3.59–6.07)	<0.05	<0.05
Medical devices	17	5.09 (3.38–7.67)	<0.05	<0.05
ICU admission	15	4.62 (2.46–8.69)	<0.05	<0.05
Patient demographic characteristics	13	1.08 (1.03–1.14)	<0.05	<0.05
Exposure to hospital care	12	1.05 (1.02–1.08)	<0.05	<0.05
Mechanical ventilation	11	1.96 (1.42–2.69)	<0.05	<0.05
CRE exposure	5	4.10 (1.46–11.52)	<0.05	0.23

[a]Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; OR, odds radio; CI, confidence interval; ICU, intensive care unit.

Plasmids responsible for carbapenem resistance often carry additional genes conferring resistance to other antibiotics, such as fluoroquinolones and aminoglycosides. This can explain why the use of these antibiotic classes is found to be a risk factor for CRE acquisition. However, this explanation cannot be used for glycopeptide antibiotics (disruption the intestinal microflora, promoting the colonization of *Enterobacteriaceae?)*

LA STORIA DELLA TERAPIA PER LE INFEZIONI DA CRE

Quali insegnamenti

ORIGINAL ARTICLE

Carbapenem Resistance, Initial Antibiotic Therapy, and Mortality in *Klebsiella pneumoniae* Bacteremia: A Systematic Review and Meta-Analysis

2017

Philipp P. Kohler, MD, MSc[1,2,3,a] Cheryl Volling, MD[1,a] Karen Green, MSc[1] Elizabeth M. Ulleryk[1,4]

Study or Subgroup	Carbapenem-resistant Events	Total	Carbapenem-susceptib Events	To
Daikos 2009	16	67	15	
Mouloudi 2010	25	37	9	
Ben-David 2011	29	42	25	
Lee 2012	18	41	20	
Liu 2012	15	25	20	
Qureshi 2012	9	19	14	
Hussein 2013	45	103	62	
Girometti 2014*	33	92	13	
Gallagher 2014*	19	43	35	
Gomez-Simmonds 2015	17	29	7	
Trecarichi 2015*	6	13	3	
Alicino 2015*	126	349	38	
Vardakas 2015*	38	52	9	
Villegas 2016*	26	39	23	
Fraenkel-Wandel 2016	44	68	54	
Total (95% CI)		**1019**		1148
Total events	466		347	

Heterogeneity: Tau² = 0.00; Chi² = 10.44, df = 14 (P = 0.73); I² = 0%
Test for overall effect: Z = 7.77 (P < 0.00001)

*Additional data were provided by the authors, not apparent in published article

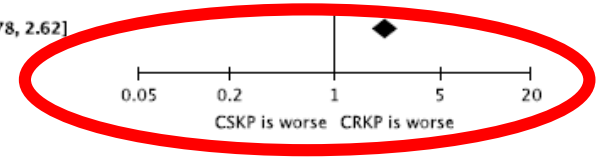


FIGURE 2. Forest plot of random-effects model looking at unadjusted mortality of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) versus carbapenem-susceptible *K. pneumoniae* (CSKP) bacteremia.

Study or Subgroup	Appropriate therapy Events	Total	Inappropriate therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Daikos 2009	22	133	9	29	19.3%	0.44 [0.18, 1.09]
Fraenkel-Wandel 2016*	21	46	60	133	25.7%	1.02 [0.52, 2.00]
Mouloudi 2010	33	58	1	1	2.6%	0.44 [0.02, 11.20]
Qureshi 2012 **	2	25	21	45	9.4%	0.10 [0.02, 0.47]
Trecarichi 2015 **	4	17	5	16	9.6%	0.68 [0.15, 3.16]
Vardakas 2015 **	22	33	17	21	12.2%	0.47 [0.13, 1.74]
Villegas 2016 **	13	43	32	58	21.2%	0.35 [0.15, 0.81]
Total (95% CI)		**355**		**303**	**100.0%**	**0.48 [0.28, 0.82]**
Total events	117		145			

Heterogeneity: Tau² = 0.18; Chi² = 9.37, df = 6 (P = 0.15); I² = 36%
Test for overall effect: Z = 2.69 (P = 0.007)

*Data provided by authors deviate slightly from data in published article
**Additional data were provided by the authors, not apparent in published article

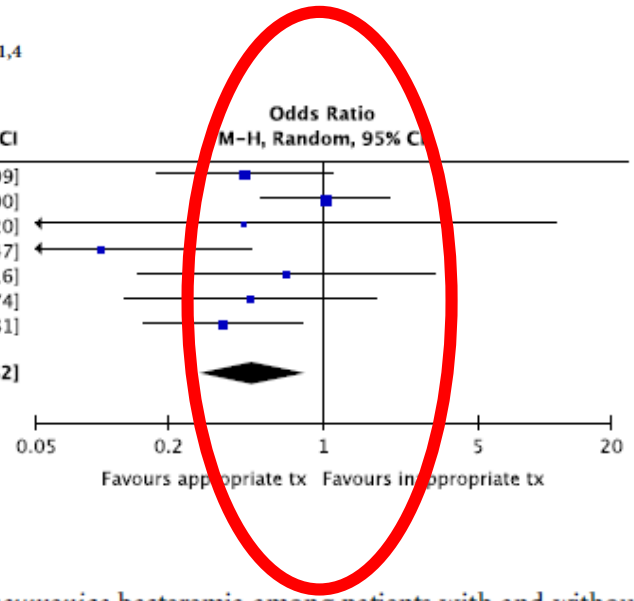


FIGURE 3. Forest plot of random-effects model looking at mortality of *Klebsiella pneumoniae* bacteremia among patients with and without initial antibiotic treatment (IAT).

American Journal of Infection Control ■■ (2018) ■■-■■

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Clinical epidemiology of carbapenem-resistant gram-negative sepsis among hospitalized patients: Shifting burden of disease?

Nicholas S. Britt PharmD, MS [a,1,*], David J. Ritchie PharmD, FCCP [a,b], Marin H. Kollef MD, FACP, FCCP [c], Carey-Ann D. Burnham PhD [d], Michael J. Durkin MD, MPH [e], Nicholas B. Hampton PharmD [f], Scott T. Micek PharmD, FCCP [a,b]

Table 2

Multivariable Cox proportional hazards models of factors associated with hospital survival in carbapenem-resistant gram-negative sepsis

Factor (n = 448)	Adjusted Hazard Ratio* (95% CI)	*P*-value
Model 1†		
CRNE infection‡	1.08 (0.62-1.87)	0.799
Length of stay (days)§	1.01 (0.98-1.01)	0.052
Genitourinary infection	0.42 (0.16-1.08)	0.071
Mechanical ventilation	3.06 (1.15-8.15)	0.025
Vasopressor requirement	3.98 (1.82-8.72)	0.001
Immunosuppression	1.51 (0.96-2.37)	0.072
Charlson comorbidity index	1.13 (1.07-1.20)	<0.001
Model 2‖		
Time to appropriate treatment (hours)¶	1.01 (1.01-1.02)	0.013
Genitourinary infection	0.23 (0.10-0.59)	0.002
Vasopressor requirement	9.75 (4.39-21.7)	<0.001
Immunosuppression	1.82 (1.15-2.87)	0.010
Charlson comorbidity index	1.14 (1.07-1.21)	<0.001

LA STORIA DELLA TERAPIA PER LE INFEZIONI DA CRE

1. Mortalità superiore dei ceppi di Klebsiella CRE rispetto ai non resistenti
2. La terapia appropriata si correla a migliore sopravvivenza
   - numero di agenti attivi su CRE?
   - tempo di inizio della terapia appropriata?

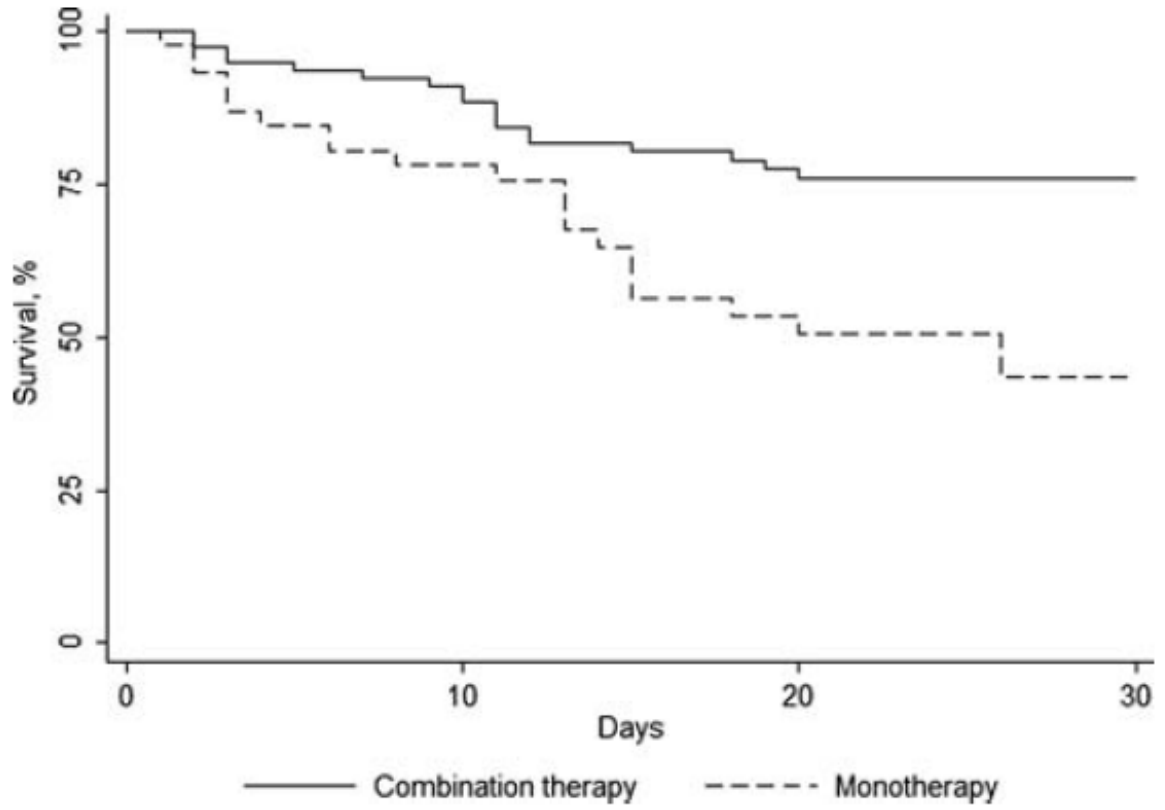


Figure 2. Kaplan-Meier curves showing the impact of combination therapy (solid line) versus monotherapy (dotted line) on 30-day mortality of patients with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* isolate bloodstream infections ($P = .002$).

MAJOR ARTICLE

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

2012

Mario Tumbarello,[1] Pierluigi Viale,[2] Claudio Viscoli,[3] Enrico Maria Trecarichi,[1] Fabio Tumietto,[2] Anna Marchese,[4] Teresa Spanu,[5] Simone Ambretti,[6] Francesca Ginocchio,[3] Francesco Cristini,[2] Angela Raffaella Losito,[1] Sara Tedeschi,[2] Roberto Cauda,[1] and Matteo Bassetti[3,7]

Mortality: 25 of the 46 (54.3%) whose regimens were classified as monotherapy and 27 of the 79 (34.1%) who were on combination regimens (P = 0.02)

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)

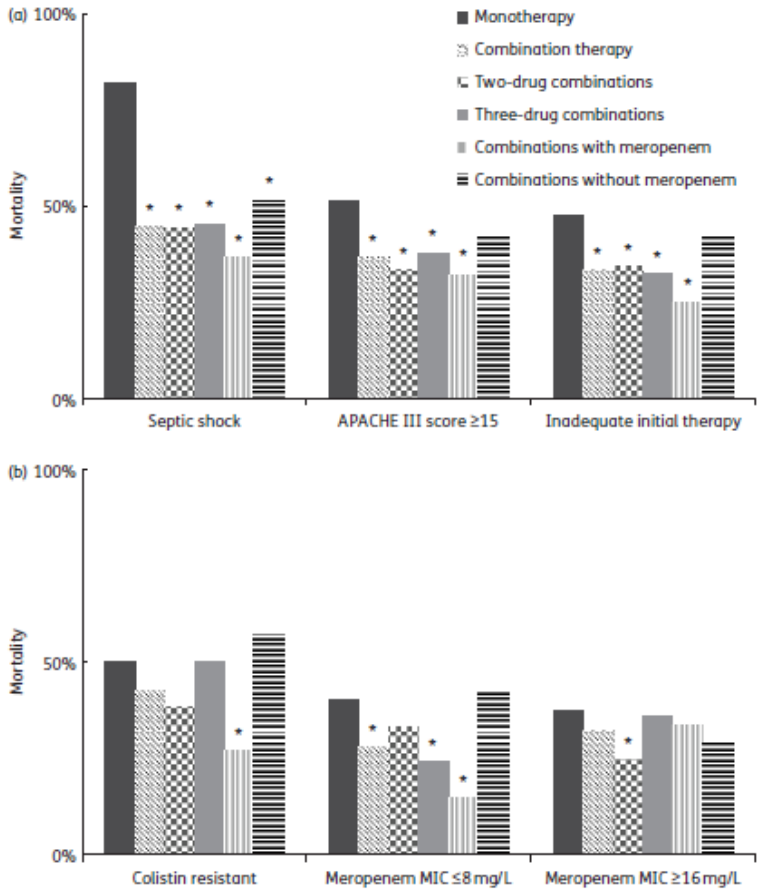
Abbreviation: MIC, minimum inhibitory concentration.

J Antimicrob Chemother
doi:10.1093/jac/dkv086

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)



- Superiorità della terapia combinata, soprattutto nelle infezioni gravi (BSI e polmoniti)
- Meropenem con MIC >16 mg/l non più efficace nella combinazione
- Ceppi colistino-R

Table 5. Multivariate analysis of risk factors for 14 day mortality in patients with infections caused by KPC-Kp

Variable	*P* value	OR (95% CI)
Combination therapy	0.001	0.52 (0.35–0.77)
BSI	<0.001	2.09 (1.34–3.29)
Septic shock at infection onset	0.001	2.45 (1.47–4.08)
APACHE III score	<0.001	1.05 (1.04–1.07)
Chronic renal failure	<0.001	2.27 (1.44–3.58)
Colistin-resistant isolate	0.001	2.18 (1.37–3.46)
Inadequate empirical antimicrobial therapy	0.04	1.48 (1.01–2.18)

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Combination Regimens for Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections

A. Gomez-Simmonds,[a] B. Nelson,[b] D. P. Eiras,[c,m] A. Loo,[b] S. G. Jenkins,[c] S. Whittier,[a] D. P. Calfee,[b,c] M. J. Satlin,[c] C. J. Kubin,[a,b]
F. Y. Furuya[a,b]

Table 5: Multivariable analysis of factors associated with 30-day mortality **2016**

Variables	Odds ratio of 30-day mortality	95% CI	p-value[§]
CCIS ≥4	1.9	0.8-4.5	0.1
Immunosuppression	0.4	0.2-1.0	0.04*
PBS ≥4	7.7	3.2-18.1	<0.0001*
SAA without a BL (reference)[§]			
SAA plus a BL[§]	0.6	0.2-2.1	0.4
MAA without a BL[§]	1.8	0.6-5.6	0.3
MAA plus a BL[§]	1.1	0.3-3.6	0.9

[§]Overall p-value 0.4

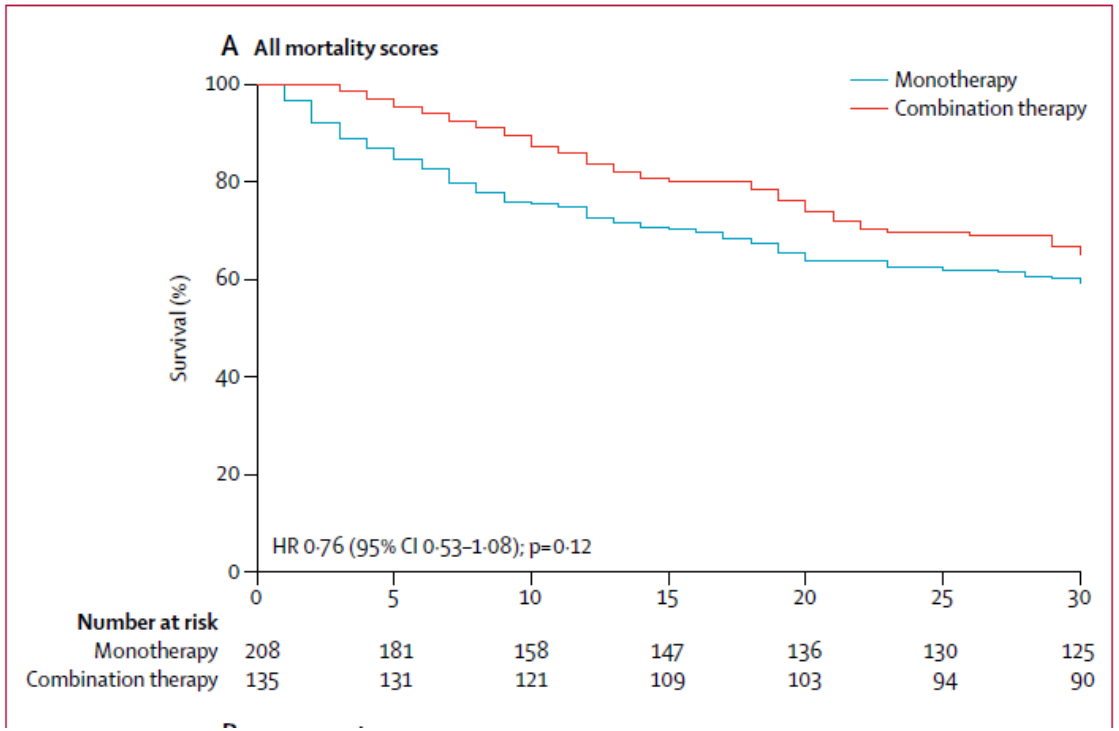
MAA multiple active agents

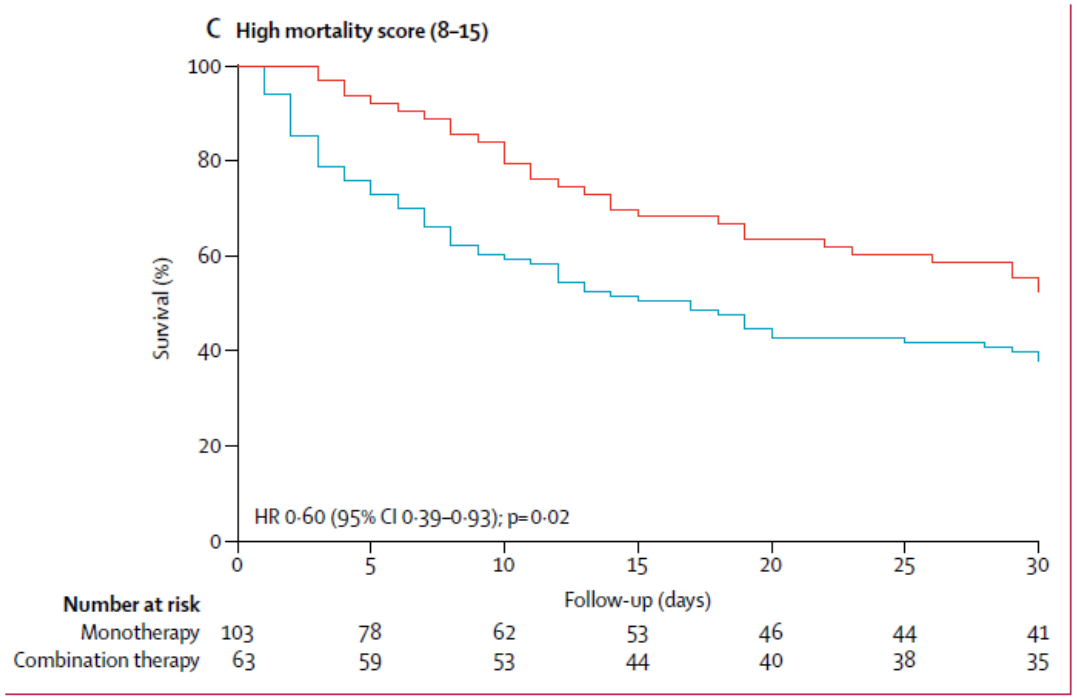
- >90% pz con MIC al meropenem≥16
- Non differenze di mortalità nei diversi sottogruppi

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

Belén Gutiérrez-Gutiérrez, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†*

- Nessuna differenza di mortalità tranne nel gruppo High Score





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	Crude analysis		Adjusted analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (per year)	1·00 (1·00–1·01)	0·32	..	..
Male sex	0·93 (0·70–1·24)	0·62	..	..
Klebsiella pneumoniae	1·29 (0·83–2·02)	0·25	..	..
OXA-type carbapenemase	1·43 (1·00- 2·05)	0·05	..	..
Nosocomial acquisition	1·83 (1·06- 3·16)	0·03	..	..
Source other than urinary or biliary tracts†	2·12 (1·37- 3·29)	0·0009	1·72 (1·09–2·72)	0·02
ICU admission	1·55 (1·16–2·08)	0·003	..	..
Charlson comorbidity index score (per unit)	1·10 (1·05–1·16)	<0·0001	1·13 (1·07–1·20)	<0·0001
Mechanical ventilation	1·76 (1·32–2·34)	<0·0001	..	..
Mental status: not alert	2·45 (1·82–3·29)	<0·0001	..	..
Chronic kidney disease	1·33 (0·97–1·84)	0·08	..	..
Chronic liver disease	1·58 (1·08–2·31)	0·02	..	..
Leukaemia or metastatic cancer	1·61 (1·12–2·31)	0·009	..	..
Pitt bacteraemia score (per unit)	1·17 (1·13–1·22)	<0·0001	1·09 (1·04–1·15)	0·0003
Severe sepsis or septic shock	3·87 (2·78–5·39)	<0·0001	3·11 (2·14–4·51)	<0·0001
Early appropriate therapy (started in ≤2 days after infection)	0·84 (0·59–1·21)	0·35		
Appropriate therapy (started in ≤5 days after infection)	0·44 (0·33–0·61)	<0·0001	0·45 (0·33–0·62)	<0·0001
High-mortality-risk centre	2·25 (1·69–2·99)	<0·0001	2·37 (1·74–3·22)	<0·0001
Study period 2004–11 (reference 2012–13)	1·52 (1·09–2·13)	0·01	1·43 (1·02–2·01)	0·04

HR=hazard ratio. OXA=oxacillinase. ICU=intensive care unit. *All variance inflation factor values of the variables included in the final multivariate model were less than 1·4. We included variables with a univariate p value of 0·2 or less for mortality in the initial model. †Biliary tract infections included cholecystitis and cholangitis.

Table 2: **Univariate and multivariate Cox regression analyses for mortality of patients with bacteraemia due to carbapenemase-producing Enterobacteriaceae**

BSI da CRE dal 2013

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

Variables	N=139
Age, mean, years (SD)	68.4 (14.0)
Males (%)	87 (62.6)
N. of comorbidities	2.13 (1.22)
Ward	
- Medical	78 (56.2)
- Surgical	54 (38.8)
- ICU	7 (5.0)
Invasive procedures in the 30 days before (%)	41 (29.5)
SOFA, mean (SD)	3.1 (2.2)
Source of infection	
- Biliary tract	24 (17.3)
- CVC	25 (18.0)
- Pneumonia	24 (17.3)
- Abdominal abscess/Thoracic abscess	18 (12.9)
- Pression ulcer	2 (1.4)
- Urinary tract	32 (23.0)
	4 (2.9)

Variables	
First line appropriateness (%)	118 (84.9)
Number of active drugs at definitive therapy regimen	
- 0	5 (3.6)
- 1	90 (64.7)
- 2	36 (25.9)
- 3	8 (5.8)
Double carbapenem	19 (13.7)
Colistin monotherapy	18 (12.9)
LOS, median (IQR)	23 (15-43)
Ritardo >2 gg Tx efficace (%)	38 (27.3)
Duration of therapy, median (IQR), days	15 (12-22)
Recurrence of KPC sepsis	13 (9.3)
30-day mortality (%)	28 (20.1)
60-day mortality (%)	43 (30.9)

Variabili correlate alla mortalità a 30 giorni

Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.06 (1.03-1.10)	<0.0001	1.05 (1.01-1.09)	0.008
ICU in the 90 days before (%)	0.41 (0.18-0.91)	0.03	0.52 (0.21-1.27)	0.15
SOFA, mean (SD)	1.19 (1.04-1.37)	0.01	1.17 (1.01-1.36)	0.04
Number of active drugs at definitive therapy regimen	1.19 (0.69-2.07)	0.52	1.32 (0.72-2.42)	0.37
Ritardo per la terapia efficace, median (IQR), days*	1.23 (1.01-1.49)	0.04	1.24 (1.02-1.52)	0.035

QUALI ACCOMPANYING DRUG

Journal of Antimicrobial Chemotherapy Advance Access published October 25, 2014

J Antimicrob Chemother
doi:10.1093/jac/dku432

Journal of Antimicrobial Chemotherapy

Gentamicina

Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*

Marcelino Gonzalez-Padilla[1]†, Julián Torre-Cisneros[1,2]*†, Francisco Rivera-Espinar[3], Antonio Pontes-Moreno[3], Lorena López-Cerero[2,4,5], Alvaro Pascual[2,4,5], Clara Natera[1], Marina Rodríguez[3], Inmaculada Salcedo[6], Fernando Rodríguez-López[2,7], Antonio Rivero[1] and Jesús Rodríguez-Baño[2,4,5]

L'uso della gentamicina si associava ad una riduzione del 41.2% della mortalità a 30 giorni

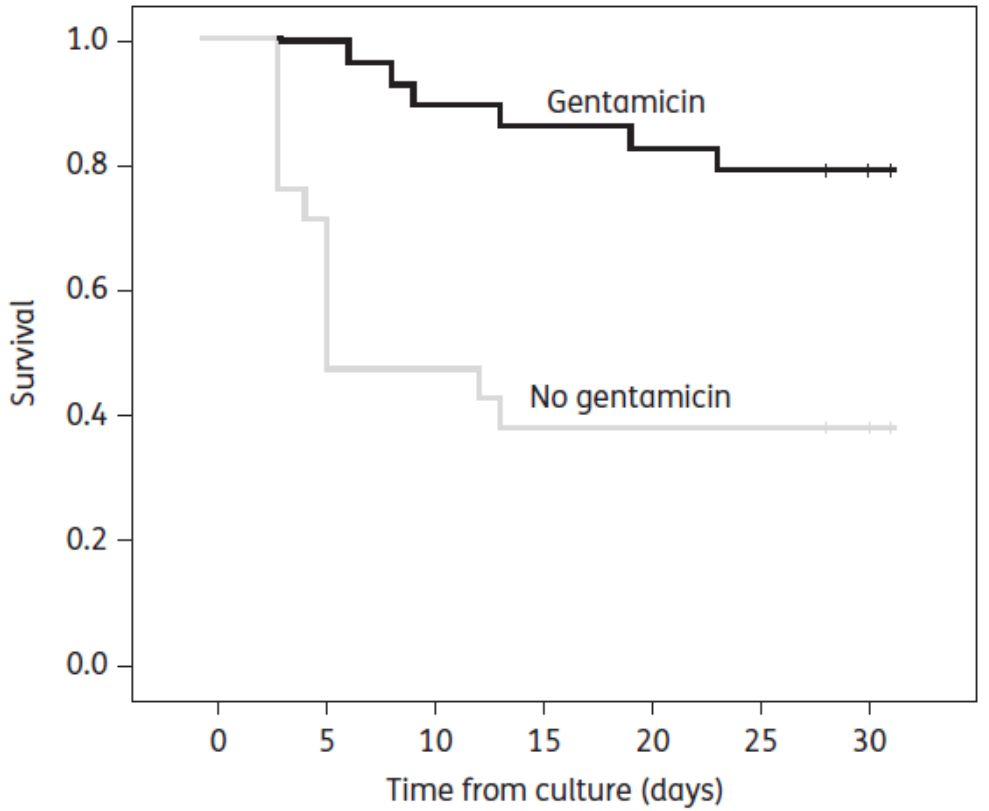

Figure 1. Kaplan–Meier curves showing the impact of targeted treatment with gentamicin on survival at 30 days in patients with severe infection caused by carbapenem-resistant and colistin-resistant *K. pneumoniae* (log-rank test 11.9, $P = 0.001$).

Fosfomicina

Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria

Fosfomycin was administered intravenously at a median dose of 24 g/day for a median of 14 days, mainly in combination with colistin or tigecycline. Clinical outcome at day 14 was successful in 54.2% of patients, whilst failure, indeterminate outcome and superinfection were documented in 33.3%, 6.3% and 6.3%, respectively.

Pontikis K et al IJAA 2016

Letter to the Editor

Fosfomycin for Multidrug Treatment of *Klebsiella pneumoniae* Carbapenemase Bacteremia

Annals of Pharmacotherapy
2015, Vol. 49(3) 366–367
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DOI: 10.1177/1060028014564395
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Intravenous Fosfomycin Treatment for Carbapenem-Resistant *Klebsiella pneumoniae* in the United States

Annals of Pharmacotherapy
1–2
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DOI: 10.1177/1060028015598126
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- Mai in monoterapia
- Attiva anche su MRSA
- Può subire l'azione di molti meccanismi di resistenza
- Effetto sinergico con altri antibiotici
- Quale test di sensibilità?

De Pascale *et al. Critical Care* 2014, **18**:R90
http://ccforum.com/content/18/3/R90

CRITICAL CARE

RESEARCH Open Access

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

Gennaro De Pascale[1*], Luca Montini[1], Mariano Alberto Pennisi[1], Valentina Bernini[1], Riccardo Maviglia[1], Giuseppe Bello[1], Teresa Spanu[3], Mario Tumbarello[2] and Massimo Antonelli[1]

Tigeciclina

Table 3 Logistic regression analysis of factors associated with clinical cure in 63 patients with ventilator-associated pneumonia

Variable	Multivariate analysis		
	Odds ratio	95% CI	*P*-value
SOFA score at infection occurrence	0.66	0.51, 0.87	0.003
Initial inadequate treatment	0.18	0.05, 0.68	0.01
High-dose tigecycline group	6.25	1.59, 24.57	0.009

SOFA, sequential organ failure assessment.

Doppio carbapenemico

AAC
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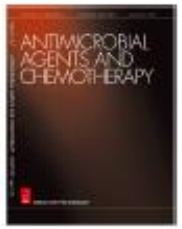
LETTER TO THE EDITOR



Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

Giancarlo Ceccarelli,[a] Marco Falcone,[b] Alessandra Giordano,[a] Maria Lina Mezzatesta,[c] Carla Caio,[c] Stefania Stefani,[c] Mario Venditti[a]

2013

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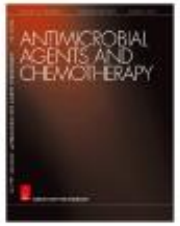


Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

Helen Giamarellou, Lambrini Galani, Fotini Baziaka, Ilias Karaiskos
5th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece

2014

J Antimicrob Chemother
doi:10.1093/jac/dku027

Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant *Klebsiella pneumoniae* bloodstream infections

Alessandra Oliva[1]†, Alessandra D'Abramo[1]†, Claudia D'Agostino[1], Marco Iannetta[1], Maria T. Mascellino[1], Carmela Gallinelli[1], Claudio M. Mastroianni[1,2]* and Vincenzo Vullo[1]

De Pascale *et al. Critical Care* (2017) 21:173
DOI 10.1186/s13054-017-1769-z

Critical Care

RESEARCH Open Access

Double carbapenem as a rescue strategy for the treatment of severe carbapenemase-producing *Klebsiella pneumoniae* infections: a two-center, matched case–control study

Gennaro De Pascale[1,6*], Gennaro Martucci[2], Luca Montini[1], Giovanna Panarello[2], Salvatore Lucio Cutuli[1], Daniele Di Carlo[3], Valentina Di Gravio[1], Roberta Di Stefano[4], Guido Capitanio[2], Maria Sole Vallecoccia[1], Piera Polidori[4], Teresa Spanu[5], Antonio Arcadipane[2] and Massimo Antonelli[1]

Table 4 Multivariable logistic regression analysis of factors associated with 28-day mortality

Variable	*p* value	OR (95% CI)
SAPS II score	<0.01	1.08 (1.04–1.23)
SOFA score	≤0.01	1.36 (1.33–1.63)
Double carbapenem treatment	0.02	0.33 (0.13–0.87)

We included all variables in the multivariable logistic regression if they reached $p \leq 0.1$ on univariate analysis. A stepwise selection procedure was used to select variables for inclusion in the final model
ROC curve analysis was used to assess the goodness of the final logistic regression model (AUC ± SE = 0.85 ± 0.034 with 95% CI 0.78–0.91; chi-square statistics $p < 0.001$)
AUC area under the curve, *OR* odds ratio, *ROC* receiver operating characteristic, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment, *SE* standard error

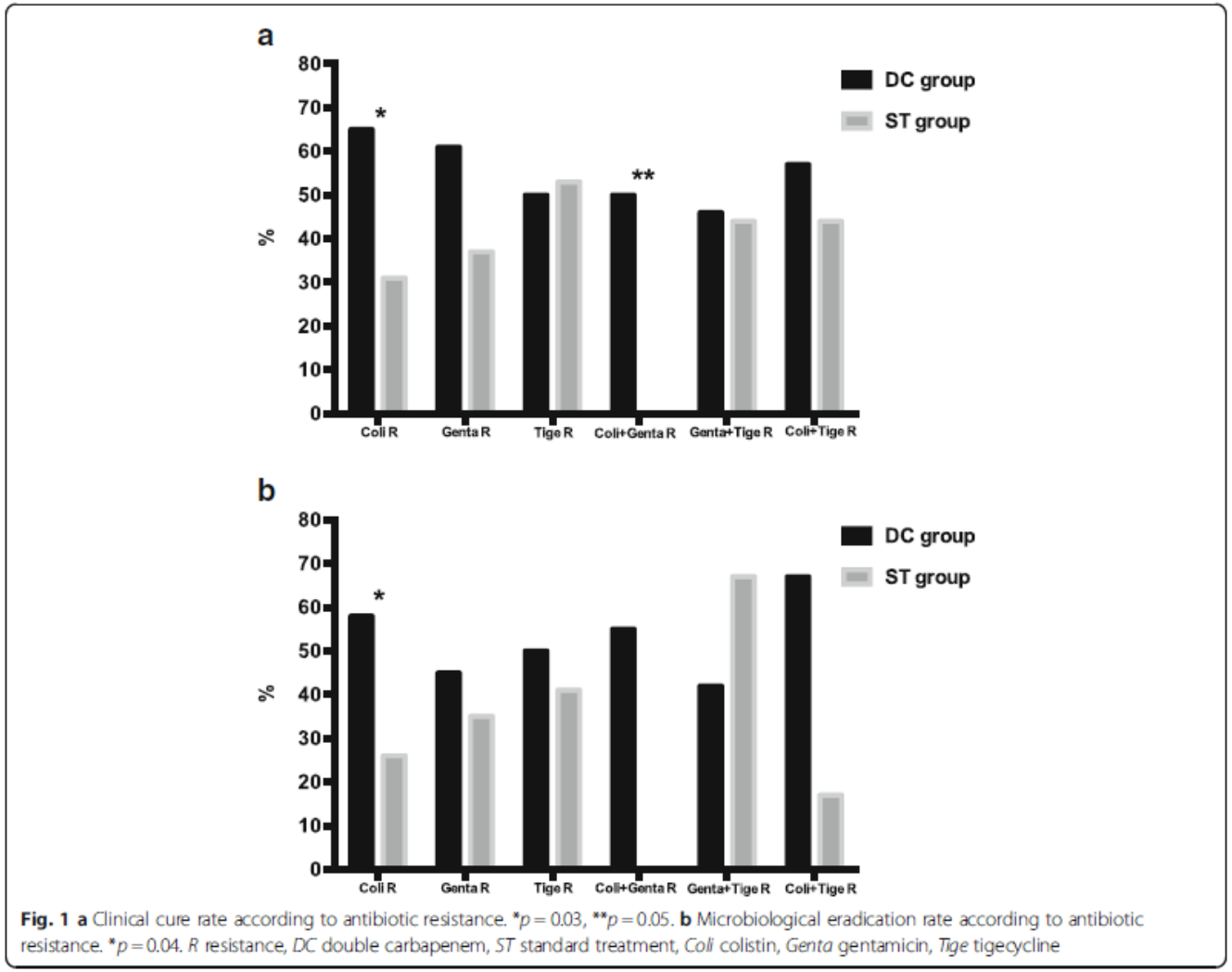


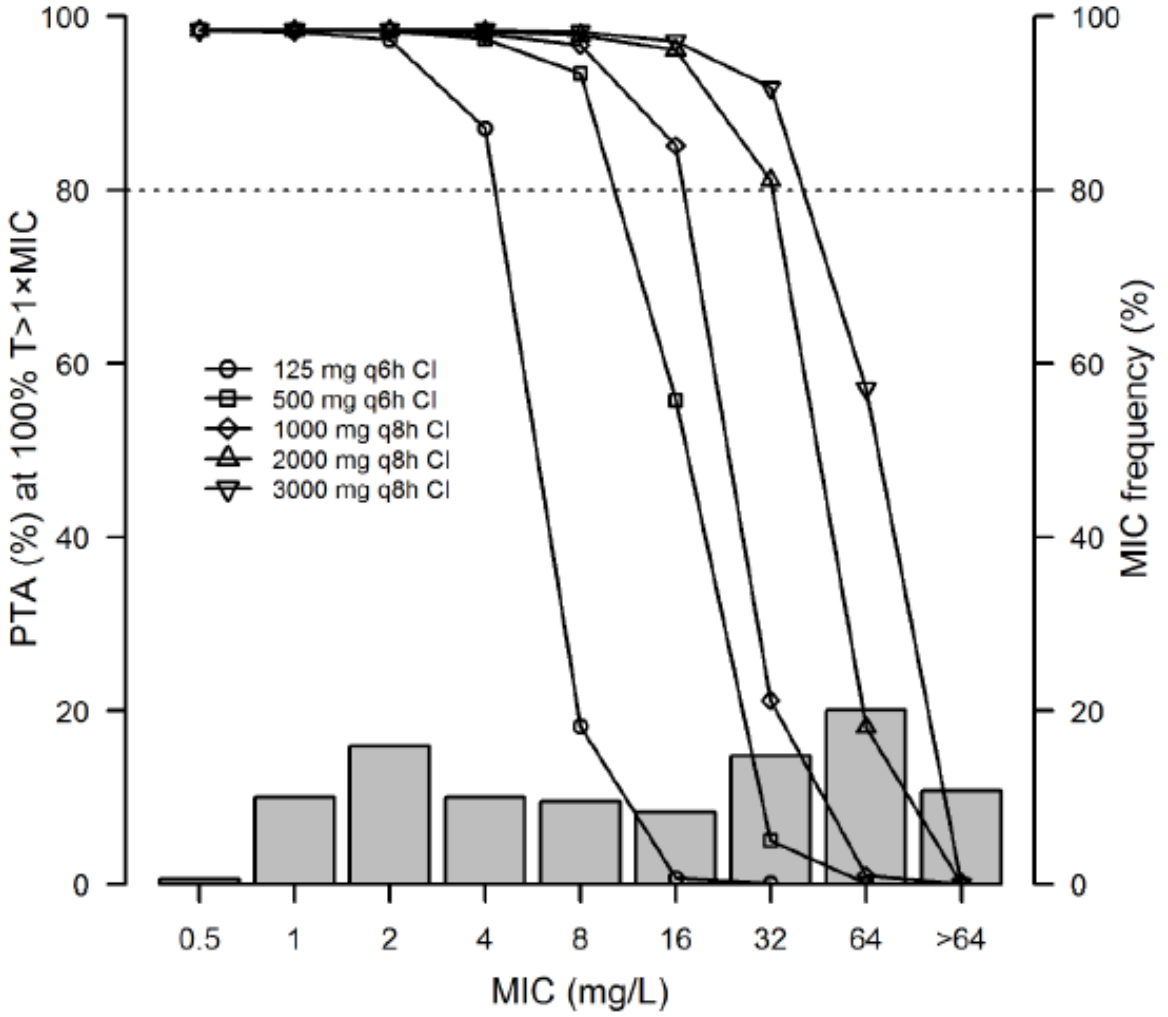
Fig. 1 **a** Clinical cure rate according to antibiotic resistance. *$p = 0.03$, **$p = 0.05$. **b** Microbiological eradication rate according to antibiotic resistance. *$p = 0.04$. *R* resistance, *DC* double carbapenem, *ST* standard treatment, *Coli* colistin, *Genta* gentamicin, *Tige* tigecycline

Carbapenemi ad alto dosaggio

1 **Population Pharmacokinetics of High Dose Continuous Infusion Meropenem and**
2 **Considerations for the Use in the Treatment of Infections due to KPC-Producing *Klebsiella***
3 ***pneumoniae***
4
5 **Piergiorgio Cojutti,[a,b] Assunta Sartor,[c] Elda Righi,[d] Claudio Scarparo,[c] Matteo Bassetti,[b,d]**
6 **Federico Pea[a,b*]**
7

AAC 2017

Per ceppi con MIC al Meropenem ≥32 mg/l sono necessarie dosaggi di 3g ogni 8 ore per raggiungere una PTA adeguata (100%$T_{>1xMIC}$)



1 **Population Pharmacokinetics of High Dose Continuous Infusion Meropenem and**
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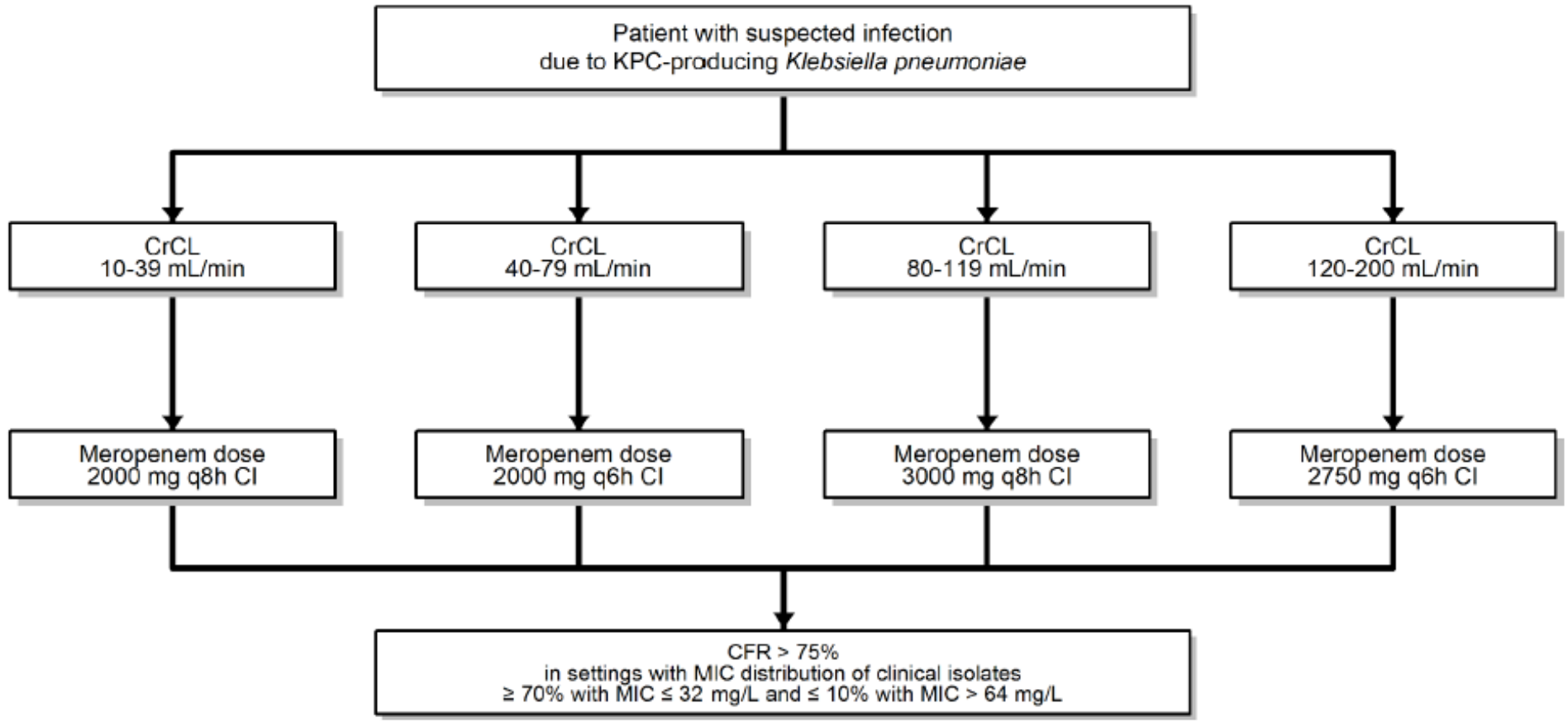
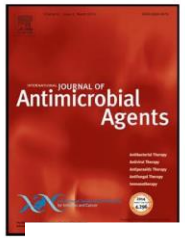
6 **Federico Pea[a,b,*]**
7

AAC 2017



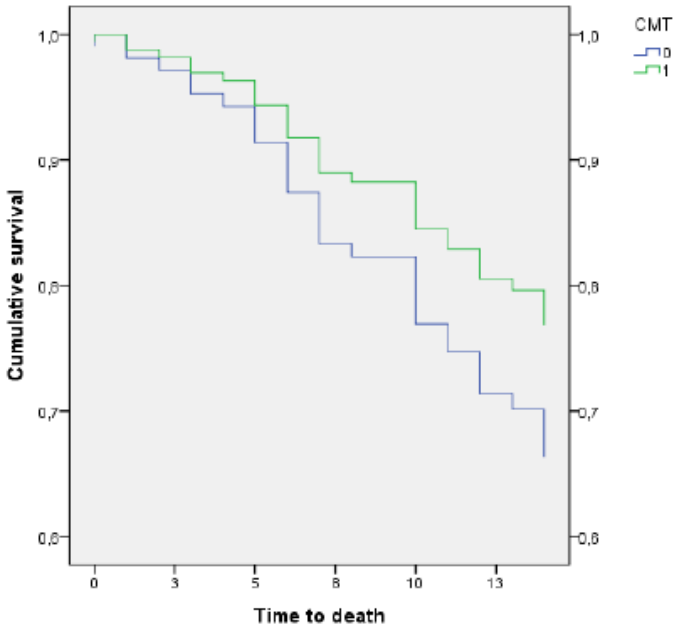


Title: Effect of combination therapy containing a high dose carbapenem on mortality in patients with carbapenem-resistant *klebsiella pneumoniae* bloodstream infection

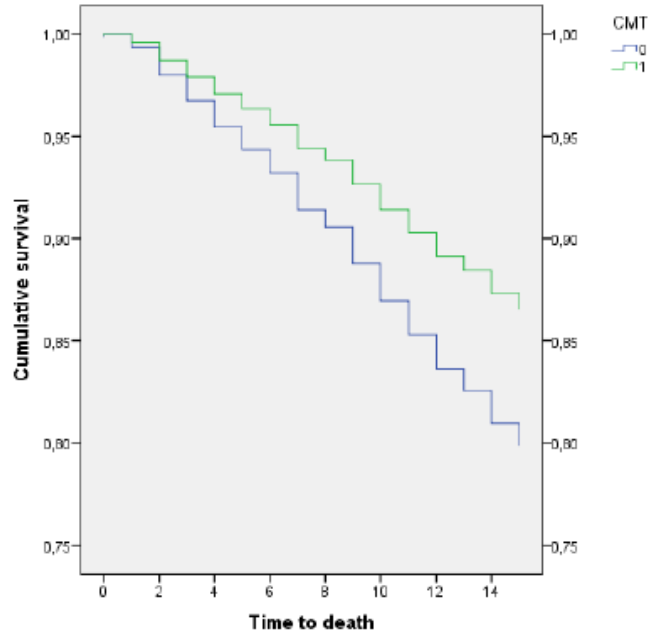
Author: Maddalena Giannella, Enrico Maria Trecarichi, Daniele Roberto Giacobbe, Francesco Giuseppe De, Matteo Bassetti, Alessandro Bartoloni, Michele Bartoletti, Angela Raffaella Losito, Valerio del Bono, Silvia Corcione, Sara Tedeschi, Francesca Raffaelli, Carolina Saffioti, Teresa Spanu, Gian Maria Rosso Marchese, Simone Ambretti, Roberto Cauda, Claudio Viscoli, Russell Edward Lewis, I Viale, Mario Tumbarello, Italian Study Group on Resistant Infections of the Società Ita Terapia Antinfettiva (ISGRI-SITA)

Meropenem 2 g ogni 8 ore

Panel A: MIC ≤8 mg/L



Panel B: MIC ≥16 mg/L



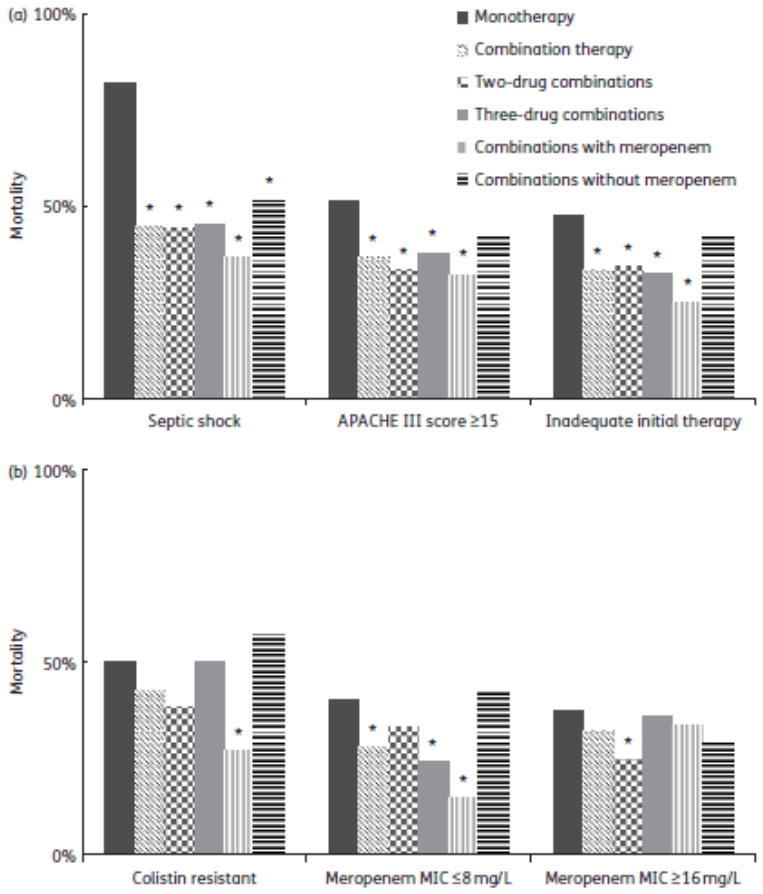
CMT: combination with meropenem treatment: 0 no, 1 yes.

Panel A and Panel B show cumulative survival at 14 days from CR-KP BSI onset for patients receiving or not carbapenem combination therapy, it was adjusted for all the covariates included into the Cox regression model and the propensity score. The model was further stratified according with the meropenem MIC ≤8 mg/L (Panel A), MIC ≥16 mg/L (Panel B), the overall aHR for the variable carbapenem combination therapy (CMT) was: 0.63, 95%CI 0.41-0.96, p=0.03.

LA STORIA DELLA TERAPIA PER LE INFEZIONI DA CRE

1. Mortalità superiore dei ceppi di Klebsiella CRE rispetto ai non resistenti
2. La terapia appropriata si correla a migliore sopravvivenza
   - numero di agenti attivi su CRE?
   - tempo di inizio della terapia appropriata?
3. La terapia combinata ***potrebbe*** essere correlata a migliore sopravvivenza
   - Alcuni accompanying drug sono associati a migliori outcomes **?**
   - Dosaggi elevati

Colistino-resistenza



J Antimicrob Chemother
doi:10.1093/jac/dkv086

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)

Table 5. Multivariate analysis of risk factors for 14 day mortality in patients with infections caused by KPC-Kp

Variable	*P* value	OR (95% CI)
Combination therapy	0.001	0.52 (0.35–0.77)
BSI	<0.001	2.09 (1.34–3.29)
Septic shock at infection onset	0.001	2.45 (1.47–4.08)
APACHE III score	<0.001	1.05 (1.04–1.07)
Chronic renal failure	<0.001	2.27 (1.44–3.58)
Colistin-resistant isolate	0.001	2.18 (1.37–3.46)
Inadequate empirical antimicrobial therapy	0.04	1.48 (1.01–2.18)

Colistino-resistenza

Predictors of outcome in ICU patients with septic shock caused by *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*

Marco Falcone, Alessandro Russo, Alessandra Iacovelli, Giovanni Restuccia, Giancarlo Ceccarelli, Alessandra Giordano, Alessio Farcomeni, Andrea Morelli, Prof. Mario Venditti

2016

Table 2. Characteristics of antibiotic regimens used during KPC-Kp infections among survived patients compared to non-survivors.

ANTIBIOTIC THERAPY*	Surviving	Non-surviving	
Colistin + Meropenem			
Colistin + Tigecycline			
Tigecycline + Gentamicin			
Meropenem + Tigecycline			
Colistin + Tigecycline + Meropenem			
Tigecycline + Meropenem + Fosfomycin			
Colistin + Tigecycline + Imipenem			
Colistin + Tigecycline + Rifampicin			
Meropenem + Ertapenem + Colistin			
Colistin + Tigecycline + Meropenem + G			
No use of *in vitro* active antibiotics			
Only one *in vitro* active antibiotic used wi			
Two or more *in vitro* active antibiotics use			
Definitive therapy with <2 antibiotics disp			
Definitive therapy with 2 or more antibiotics displaying *in vitro* activity	57 (85.1)	7 (15.9)	**<0.001**

Legend. KPC-Kp: *Klebsiella pneumoniae*

Table 3. Cox regression analysis of factors associated with death

VARIABLES	HR	CI 95%	*p*
Colistin-containing antibiotic regimen	0.21	0.05-0.72	<0.001
Two or more *in vitro* active antibiotics as definitive therapy	0.08	0.02-0.21	<0.001
Control of removable source of infection	0.14	0.04-0.25	<0.001
Colistin-resistant strain	8.09	3.14-11.23	0.001
Intra-abdominal source of infection	2.92	2.11-4.12	0.002

Legend. KPC-Kp: *Klebsiella pneumoniae* carbapenem-resistant; ICU: intensive care unit.

LA STORIA DELLA TERAPIA PER LE INFEZIONI DA CRE

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   - Alcuni accompanying drug sono associati a migliori outcomes **?**
   - Dosaggi elevati
4. L'ampio uso di colistina si correla all'incremento della colistino-resistenza

LA STORIA DELLA TERAPIA PER LE INFEZIONI DA CRE

LIMITI

- Mancanza di STUDI RANDOMIZZATI
- Epidemiologia CRE eterogenea
  - Popolazioni diverse
  - Metodologia diversa
  - MIC antibiotici diverse
  - Specie batteriche diverse

Clinical Microbiology and Infection xxx (2018) 1–7

Contents lists available at ScienceDirect

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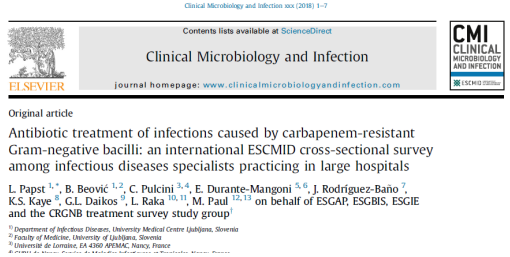
Original article

Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infectious diseases specialists practicing in large hospitals

L. Papst [1, *], B. Beović [1, 2], C. Pulcini [3, 4], E. Durante-Mangoni [5, 6], J. Rodríguez-Baño [7], K.S. Kaye [8], G.L. Daikos [9], L. Raka [10, 11], M. Paul [12, 13] on behalf of ESGAP, ESGBIS, ESGIE and the CRGNB treatment survey study group[†]

[1] *Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia*
[2] *Faculty of Medicine, University of Ljubljana, Slovenia*
[3] *Université de Lorraine, EA 4360 APEMAC, Nancy, France*
[4] *CHRU de Nancy, Service de Maladies Infectieuses et Tropicales, Nancy, France*

FATTORI CONSIDERATI IMPORTANTI PER DECIDERE QUALE TERAPIA per CRE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[1] Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Slovenia
[3] Université de Lorraine, EA 4360 APEMAC, Nancy, France

Table 1
Importance of different factors when choosing an antibiotic for treating infections caused by carbapenem-resistant Gram-negative bacilli

Factor	*n* (%), *N* = 110		
	Not important	Moderately important	Very important
Source of infection (e.g. pneumonia, urinary tract infection etc.)	1 (0.9)	15 (13.6)	94 (85.5)
Severity of the disease	2 (1.8)	15 (13.6)	93 (84.5)
Immune status of the patient	0 (0)	50 (45.5)	60 (54.5)
Renal or hepatic impairment	2 (1.8)	53 (48.2)	55 (50)
Type of isolated microorganism (e.g. *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, etc.)	1 (0.9)	25 (22.7)	84 (76.4)
Type of carbapenemase (e.g. *Klebsiella pneumoniae* carbapenemase, New Delhi metallo-β-lactamase etc.)	14 (12.7)	38 (34.5)	58 (52.7)
Minimum inhibitory concentration (MIC) for the antibiotic	2 (1.8)	17 (15.5)	91 (82.7)
Pharmacokinetic/pharmacodynamic profile of the antibiotic	1 (0.9)	24 (21.8)	85 (77.3)
Toxicity profile of the antibiotic	4 (3.6)	53 (48.2)	53 (48.2)
Interactions of the antibiotic with other drugs	15 (13.6)	56 (50.9)	39 (35.5)

Papst L et al, CMI 2018

Table 3
Carbapenem-containing combination regimens for carbapenem-resistant Gram-negative bacilli

Carbapenem used for combination therapy	*n* (%), *N* = 109
Doripenem	2 (1.8)
Imipenem	26 (23.9)
Meropenem	100 (91.7)
Ertapenem	7 (6.4)
Double-carbapenem combination therapy (ertapenem combined with another carbapenem)	26 (23.9)
No carbapenem-containing combinations	8 (7.3)
Carbapenem MIC at which its use is considered	*n* (%), *N* = 106
MIC ≤4 mg/L	10 (9.4)
MIC ≤8 mg/L	47 (44.3)
MIC ≤16 mg/L	20 (18.9)
MIC ≤32 mg/L	10 (9.4)
Carbapenem use regardless of the MIC value	19 (17.9)
Use of prolonged carbapenem infusion in combinations	*n* (%), *N* = 105
Yes	76 (72.4)
No	29 (27.6)

Table 4
Indications for use of combination therapy

Source of infection	*n* (%), *N* = 110
Complicated urinary tract infections	41 (37.3)
Pneumonia	92 (83.6)
Intra-abdominal infections	80 (72.7)
Skin and soft-tissue infections	42 (38.2)
Central nervous system infections	96 (87.3)
Bacteraemia of any source	91 (82.7)
Bacteria	*n* (%), *N* = 109
Carbapenem-resistant *Enterobacteriaceae*	98 (89.9)
Carbapenem-resistant extensively drug-resistant *Pseudomonas aeruginosa*	93 (85.3)
Carbapenem-resistant extensively drug-resistant *Acinetobacter baumannii*	90 (82.5)

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Original article

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[1] Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Slovenia
[3] Université de Lorraine, EA 4360 APEMAC, Nancy, France

Table 5

Most frequent antibiotic regimens for targeted treatment for infections caused by carbapenem-resistant *Enterobacteriaceae* [a]

Total $N = 114$	cUTI	Pneumonia	IAI	SSTI	CNSI	Bacteraemia
Monotherapy ($N = 57$, 50%)						
POL	20 (35.1)	18 (31.6)	10 (17.5)	12 (21.2)	7 (12.3)	17 (29.8)
TIG	5 (8.8)	9 (15.8)	20 (35.1)	20 (35.1)	3 (5.3)	8 (14)
AMG	40 (70.2)	6 (10.5)	8 (14)	7 (12.3)	3 (5.3)	14 (24.6)
FOS	19 (33.3)	1 (1.8)	1 (1.8)	0 (0)	3 (5.3)	3 (5.3)
CAZ/AVI	20 (35.1)	16 (28.1)	17 (29.8)	16 (28.1)	5 (8.8)	17 (29.8)
Double combination therapy ($N = 105$, 92.1%)						
POL + TIG	13 (10)	43 (41)	61 (58.1)	40 (38.1)	9 (8.6)	34 (32.4)
POL + CARB	53 (50.5)	63 (60)	52 (49.5)	35 (33.3)	52 (49.5)	67 (63.9)
TIG + CARB	6 (5.7)	24 (22.9)	40 (38.1)	26 (24.8)	9 (8.6)	21 (20)
TIG + AMG	9 (8.6)	12 (11.4)	32 (30.5)	26 (24.8)	3 (2.9)	18 (17.1)
AMG + FOS	34 (32.4)	8 (7.6)	8 (7.6)	8 (7.6)	7 (6.7)	18 (17.1)
Triple combination therapy ($N = 72$, 63.2%)						
POL + TIG + CARB	12 (16.7)	39 (54.2)	36 (50)	22 (30.6)	21 (29.2)	40 (55.6)
POL + TIG + AMG	9 (12.5)	17 (23.6)	17 (23.6)	6 (8.3)	6 (8.3)	21 (29.2)
POL + TIG + FOS	4 (5.6)	14 (19.4)	8 (11.1)	6 (8.3)	8 (11.1)	13 (18.1)
POL + AMG + FOS	17 (23.6)	7 (9.7)	4 (5.6)	2 (2.8)	4 (5.6)	15 (20.8)
Double CARB + POL	8 (11.1)	11 (15.3)	7 (9.7)	5 (6.9)	12 (16.7)	13 (18.1)

Abbreviations: cUTI, complicated urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft-tissue infection; CNSI, central nervous system infection; POL, polymyxin; TIG, tigecycline; AMG, aminoglycoside; FOS, fosfomycin; CAZ/AVI, ceftazidime/avibactam; CARB, carbapenem.

[a] Respondents could choose more than one treatment regimen. Detailed data on all antibiotic regimens are presented in the Supplementary material (Table S4).

Ceftazidime-avibactam

- Cefalosporina + inibitore β–lattamasi non β–lattamico
- Non attivo sulle MBL, ma attivo anche su molti ceppi di OXA-48, su ESBL e su β–lattamasi AmpC mediate
- Non attivo su *Stenotrophomonas* e *Acinetobacter*
- Approvato dopo RCT per UTI complicate e IAI
- Finora case series/cohort studies fino a 60 pz
  - Sia target therapy sia salvage
  - Sia mono che in comb

- Miglior parametro farmacocinetico %fT/MIC
- Penetrazione ELF: concentrazioni 30% quelle plasmatiche
- Metabolizzato per via renale
- Metabolismo non influenzato da insufficienza epatica
- Avibactam inibito da Probenecid
- 2,5 g ogni 8 ore (tempo di infusione 2 ore)
- Report occasionali di alterazioni neurologiche (tremor, clonie, stato epilettico non convulsivante, convulsioni, encefalopatia, coma) nei pazienti con insufficienza renale senza aggiustamento del dosaggio

Clinical Infectious Diseases

MAJOR ARTICLE

Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program

Florian M. Wagenlehner,[1] Jack D. Sobel,[2] Paul Newell,[3] Jon Armstrong,[3] Xiangning Huang,[4] Gregory G. Stone,[5] Katrina Yates,[3,a] and Leanne B. Gasink[6,b]

[1]Justus-Liebig-University, Giessen, Germany; [2]Detroit Medical Center, Michigan; [3]AstraZeneca, Alderley Park, Cheshire, and [4]AstraZeneca, Cambridge, United Kingdom; [5]AstraZeneca, Waltham, Massachusetts; and [6]AstraZeneca, Wilmington, Delaware

Results. Of 1033 randomized patients, 393 and 417 treated with ceftazidime-avibactam and doripenem, respectively, were eligible for the primary efficacy analyses; 19.6% had ceftazidime-nonsusceptible baseline pathogens. Noninferiority of ceftazidime-avibactam vs doripenem was demonstrated for the US Food and Drug Administration co-primary endpoints of (1) patient-reported symptomatic resolution at day 5: 276 of 393 (70.2%) vs 276 of 417 (66.2%) patients (difference, 4.0% [95% confidence interval {CI}, −2.39% to 10.42%]); and (2) combined symptomatic resolution/microbiological eradication at test of cure (TOC): 280 of 393 (71.2%) vs 269 of 417 (64.5%) patients (difference, 6.7% [95% CI, .30% to 13.12%]). Microbiological eradication at TOC (European Medicines Agency primary endpoint) occurred in 304 of 393 (77.4%) ceftazidime-avibactam vs 296 of 417 (71.0%) doripenem patients (difference, 6.4% [95% CI, .33% to 12.36%]), demonstrating superiority at the 5% significance level. Both treatments showed similar efficacy against ceftazidime-nonsusceptible pathogens. Ceftazidime-avibactam had a safety profile consistent with that of ceftazidime alone.

Conclusions. Ceftazidime-avibactam was highly effective for the empiric treatment of cUTI (including acute pyelonephritis), and may offer an alternative to carbapenems in this setting.

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

Elizabeth Temkin,[a] Julian Torre-Cisneros,[i,j] Bojana Beovic,[b] Natividad Benito,[c,d] Maddalena Giannella,[e] Raúl Gilarranz,[f] Cameron Jeremiah,[g] Belén Loeches,[h] Isabel Machuca,[i,j] María José Jiménez-Martín,[k] José Antonio Martínez,[l] Marta Mora-Rillo,[h] Enrique Navas,[m] Michael Osthoff,[n] Juan Carlos Pozo,[o] Juan Carlos Ramos Ramos,[h] Marina Rodriguez,[o] Miguel Sánchez-García,[k] Pierluigi Viale,[p] Michel Wolff,[q,r] Yehuda Carmeli[a,s]

Department of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israela

TABLE 1 Antimicrobial susceptibility of isolates from patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI

Antibiotic	No. of isolates tested[a]	% Susceptible
Imipenem	36	2.8[b]
Meropenem	33	0.0
Ceftazidime	38	0.0
Colistin	34	41.2
Gentamicin	37	51.4
Amikacin	38	31.6
Tigecycline	32	62.5
Fosfomycin	29	55.2

[a]Sample included 34 *K. pneumoniae*, 1 *K. oxytoca*, 1 *E. coli*, and 2 *P. aeruginosa* isolates.
[b]Patient with OXA-48-producing *E. coli* who had failed imipenem treatment (MIC not reported).

TABLE 4 Outcomes of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI, by infection site

Infection site[a]	Total no. of cases	No. (%) of cases with:			Patients with:				Mortality among patients with microbiological cure	
		Bacteremia	Life-threatening infection	Documented microbiological cure	Clinical cure		In-hospital death			
					No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
All patients	38	26 (68.4)	23 (60.5)	24 (63.2)	26 (68.4)	51.3–82.5	15 (39.5)	24.0–56.6	5 (20.8)	7.1–42.2
Intra-abdominal	15	11 (73.3)	8 (53.3)	6 (40.0)	10 (66.7)	38.4–88.2	6 (40.0)	16.3–67.7	1 (16.7)	0.4–64.1
Pneumonia[b]	7	6 (85.7)	5 (71.4)	3 (42.9)	3 (42.9)	9.9–81.6	5 (71.4)	29.0–96.3	1 (33.3)	0.8–90.6
Skin and soft tissue	4	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)	0.6–80.6	2 (50.0)	6.8–93.2	0 (0.0)	0.0–97.5
Urinary tract	3	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)	9.4–99.2	2 (66.7)	9.4–99.2	1 (50)	1.3–98.7
Primary or catheter-associated bacteremia	7	7 (100)	7 (100)	7 (100.0)	7 (100)	59.0–100	1 (14.3)	0.4–57.9	1 (14.3)	0.4–57.9
Any bacteremia	26	26 (100)	20 (76.9)	18 (69.2)	18 (69.2)	48.2–85.7	11 (42.3)	23.4–63.1	4 (22.2)	6.4–47.6
Endocarditis	2	1 (50.0)	1 (50.0)	2 (100.0)	2 (100.0)	15.8–100	1 (50.0)	1.3–98.7	1 (50)	1.3–98.7
Osteomyelitis	3	0 (0.0)	0 (0.0)	2 (66.7)	2 (66.7)	9.4–99.2	1 (33.3)	0.8–90.6	0 (0.0)	0.0–84.2
Surgical site infection	2	1 (50.0)	2 (100)	1 (50.0)	1 (50.0)	1.3–98.7	1 (50.0)	1.3–98.7	0 (0.0)	0.0–97.5
Other[c]	3	1 (33.3)	2 (66.7)	3 (100)	2 (66.7)	9.4–99.2	1 (33.3)	0.8–90.6	1 (33.3)	0.8–90.6

[a]Patients may have multiple infection sites.
[b]Pneumonia cases included 6 cases of ventilator-associated pneumonia and 1 case of hospital-acquired pneumonia.
[c]Other infection types (1 patient each) were ventriculitis/subdural abscess, prosthetic joint infection, and mucositis.

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Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant *Klebsiella pneumoniae* Bacteremia

Ryan K. Shields,[a,c] M. Hong Nguyen,[a,c] Liang Chen,[d] Ellen G. Press,[a] Brian A. Potoski,[a,c,e] Rachel V. Marini,[c] Yohei Doi,[a,c] Barry N. Kreiswirth,[d] Cornelius J. Clancy[a,b,f]

Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA[a]; XDR Pathogen Laboratory, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[b]; Antibiotic Management Program, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[c]; Public Health Research Institute Tuberculosis Center, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA[d]; Department o Pharmacy & Therapeutics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA[e]; VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA[f]

- 109 pazienti
- Studio retrospettivo
- Maggior tasso di eventi avversi nel gruppo AG o Colistina

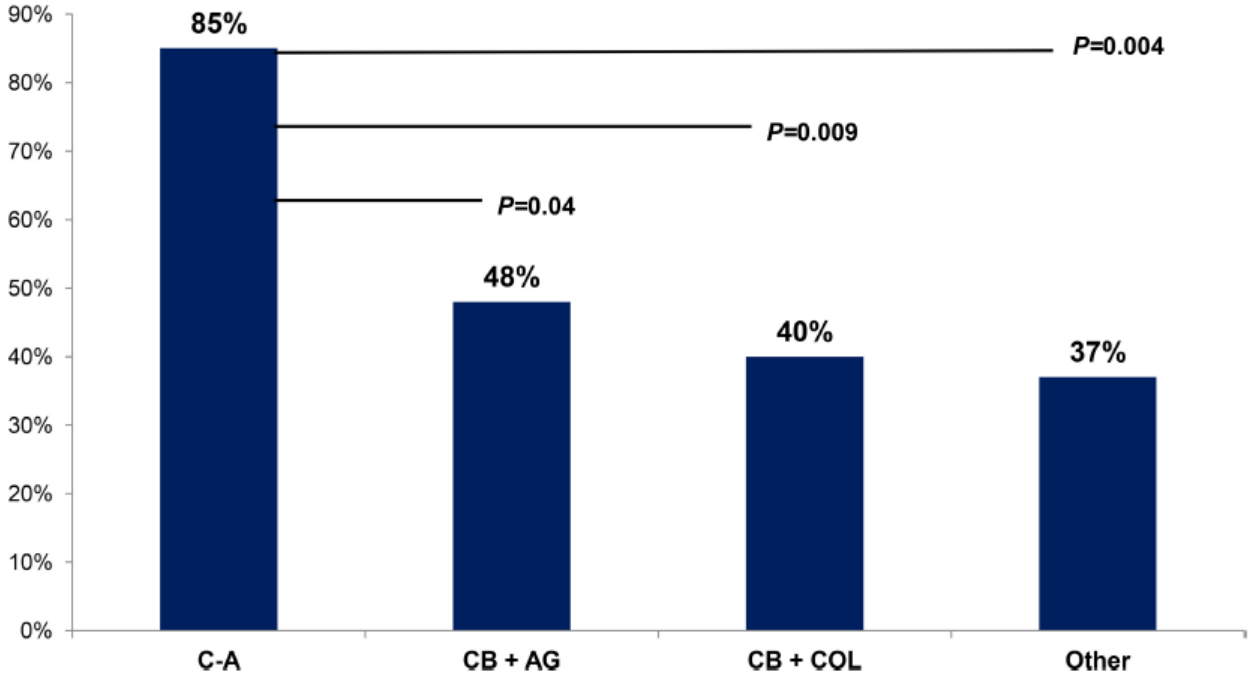

FIG 1 Rates of 30-day clinical success across treatment regimens. Among patients with carbapenem-resistant *Klebsiella pneumoniae* bacteremia, rates of clinical success were significantly higher among patients receiving ceftazidime-avibactam than among those who received a carbapenem plus aminoglycoside ($P = 0.04$) or colistin ($P = 0.009$) or other regimens ($P = 0.004$). Other regimens included aminoglycoside ($n = 11$), carbapenem ($n = 8$), colistin ($n = 4$), tigecycline ($n = 4$), and ciprofloxacin ($n = 2$) monotherapy, as well as combination regimens of colistin plus tigecycline ($n = 3$), aminoglycoside plus tigecycline ($n = 2$), and 1 each of aminoglycoside plus cefepime, aminoglycoside plus colistin plus tigecycline, colistin plus aztreonam, colistin plus cefepime, colistin plus ciprofloxacin, carbapenem plus doxycycline, and carbapenem plus tigecycline.

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Journal of Antimicrobial Chemotherapy

Efficacy and safety of ceftazidime/avibactam: a systematic review and meta-analysis

Neta Sternbach[1]†, Yaara Leibovici Weissman[1,2]†, Tomer Avni[2,3] and Dafna Yahav[2,3]*

- Nessuna differenza significativa nella mortalità a 30 gg, mortalità a fine FU, risposta clinica di ceftazidime/avibactam vs comparators (++ carbapenemi)
- Migliore risposta microbiologica di ceftazidime/avibactam vs comparators per le UTI
- Maggior tasso di sospensione in ceftazidime/avibactam per sintomi gastroenterici nei trials per IAI
- Maggior tasso di eventi avversi severi in ceftazidime/avibactam.

Clinical Infectious Diseases
MAJOR ARTICLE

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

David van Duin,[1] Judith J. Lok,[2] Michelle Earley,[2] Eric Cober,[3] Sandra S. Richter,[4] Federico Perez,[5,6] Robert A. Salata,[6] Robert C. Kalayjian,[7] Richard R. Watkins,[8,9] Yohei Doi,[10] Keith S. Kaye,[11] Vance G. Fowler Jr,[12,13] David L. Paterson,[14] Robert A. Bonomo,[5,6,15,16] and Scott Evans[2]; for the Antibacterial Resistance Leadership Group

- Studio osservazionale multicentrico (coorte CRACKLE), US
- Sia terapia combinata che mono
- Ceftazidime/Avibactam n=38 e colistina n=99; BSI 46%

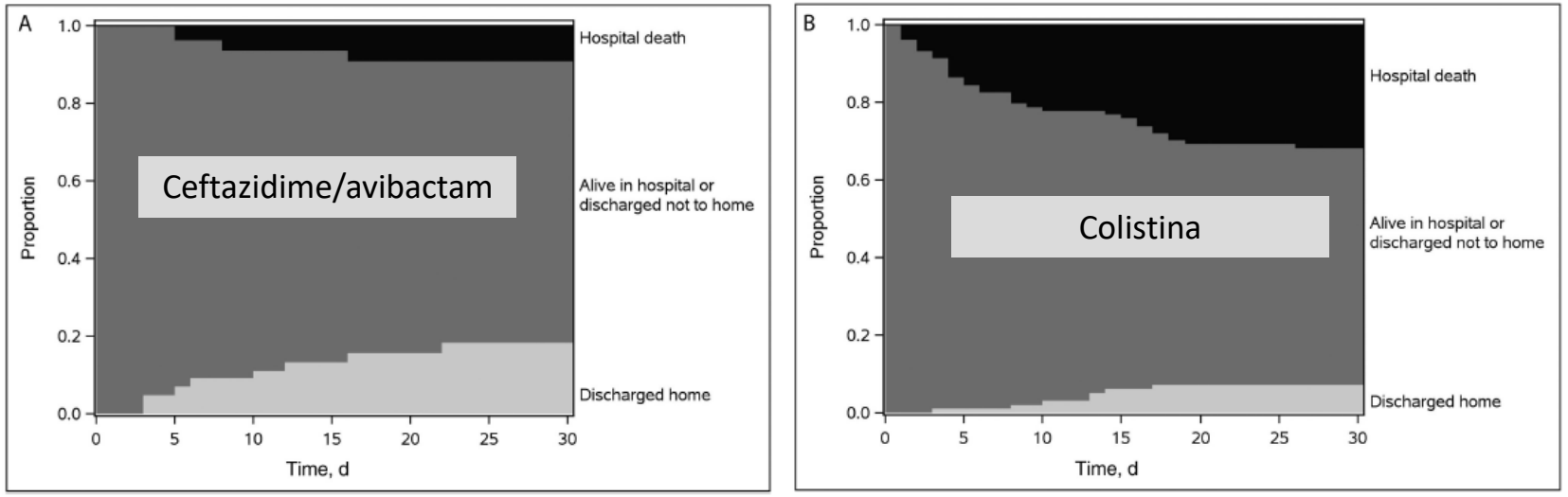

Figure 1. Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A*, Ceftazidime-avibactam group (n = 38). *B*, Colistin group (n = 99).

Open Forum Infectious Diseases

ID CASE

Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in *Klebsiella pneumoniae* Carbapenemase-Producing *K pneumoniae*: A Case Report and Review of Literature

Ryan K. Shields,[1,2] M. Hong Nguyen,[1,2] Ellen G. Press,[1] Liang Chen,[3] Barry N. Kreiswirth,[3] and Cornelius J. Clancy[1,2,4]

[1]Department of Medicine, University of Pittsburgh, Pennsylvania; [2]XDR Pathogen Laborator University of Pittsburgh Medical Center, Pennsylvania; [3]Public Health Research Institute Tuberculosis Center, New Jersey Medical School, Rutgers University, Newark; and [4]VA Pittsburgh Healthcare System, Pennsylvania

Emergenza di resistenza a ceftazidime/avibactam in circa il 10% dei casi

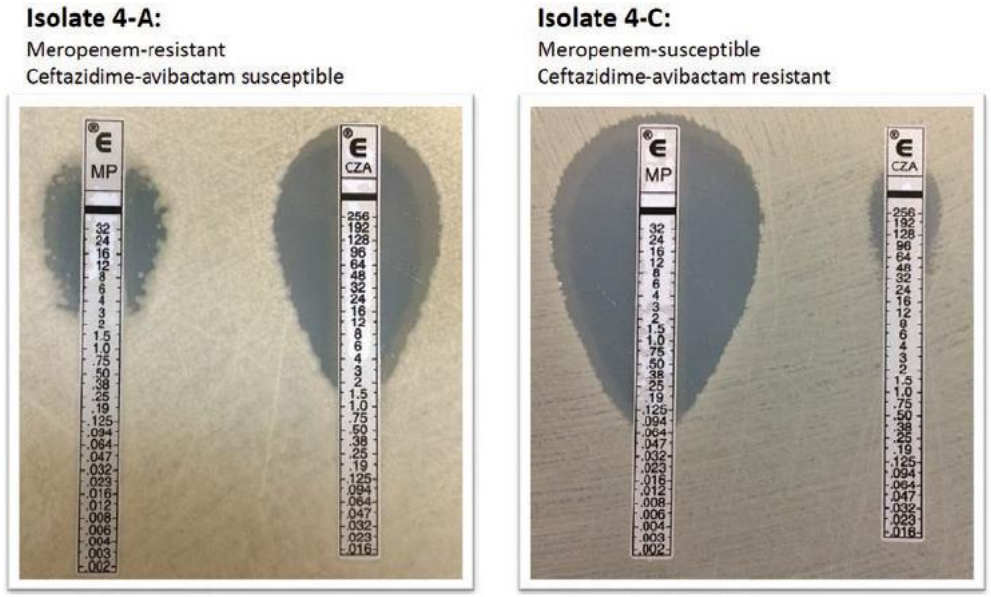

Figure 2. Restoration of meropenem susceptibility among ceftazidime-avibactam-resistant *Klebsiella pneumonia*. Etest results for meropenem and ceftazidime-avibactam against baseline isolate 4-A (left) and follow-up isolate 4-C (right).

Ceftazidime-avibactam

Monoterapia o accompanying therapy?

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REVIEW

Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing *Enterobacteriaceae*

2018

Jesús Rodríguez-Baño,[a] Belén Gutiérrez-Gutiérrez,[a] Isabel Machuca,[b] Alvaro Pascual[a]

ANTIBIOGRAMMA	BACKBONE	ACCOMPANYING
Quadro settico o comorbidità (HIGH-RISK)		
Ceftazidime/avibactam S	Ceftazidime/Avibactam + Meropenem (se MIC≤8)	Colistina o Tigeciclina o Aminoglicosidi o Fosfomicina (se l'isolato è Intermedio al backbone almeno 2 di questa lista)
Ceftazidime/avibactam R	Colistina + (Tigeciclina o Aminoglicoside o Fosfomicina)	
Ceftazidime/avibactam R e Colistina R	Tigeciclina + Aminoglicoside	Fosfomicina
Pan-resistant	Doppio carbapenemico oppure (ceftazidime/avibactam + aztreonam) + Investigational drug + test sinergia in vitro	

Colistina preferibile come accompying drug nelle VAP/HAP; **Tigeciclina** preferibile come accompying drug nelle infezioni addominali (se usata per IAI, BSI o UTI considerare il dosaggio doppio); **Aminoglicoside** preferibile come accompying drug nelle UTI (se usata per VAP/HAP considerare il dosaggio doppio); utile TDM; **Fosfomicina** preferibile come accompying drug nelle UTI o come 3° farmaco

	BACKBONE	
Quadro non settico (LOW-RISK)		
Monoterapia	Ceftazidime/Avibactam o Meropenem o Ceftazidime o Colistina o Tigeciclina o Aminoglicosidi	

Colistina preferibile come accompying drug nelle VAP/HAP; **Tigeciclina** preferibile come accompying drug nelle infezioni addominali (se usata per IAI, BSI o UTI considerare il dosaggio doppio); **Aminoglicoside** preferibile come accompying drug nelle UTI (se usata per VAP/HAP considerare il dosaggio doppio); utile TDM; **Fosfomicina** preferibile come accompying drug nelle UTI o come 3° farmaco

[a]Close clinical and microbiological follow-up is needed. If any of the following is needed, consider the source: colistin, preferred over other accompanying drugs in cases of HAP/VAP; tigecycline, to be considered mostly for cIAI (if used for HAP, BSI, or cUTI, consider double dosing); aminoglycoside, to be considered mostly for cUTI (if needed for HAP, consider a high dose), and TDM is recommended; fosfomycin, to be considered mostly for cUTI but, if needed, also as a third drug for any source. For cIAI, consider adding metronidazole except for with meropenem and tigecycline. It may be wise to reserve the newer drugs (ceftazidime-avibactam and meropenem-vaborbactam) for high-risk patients whenever possible. HAP, hospital-acquired pneumonia; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; TDM, therapeutic drug monitoring.

HIGH-RISK PATIENTS:

- Shock settico o BSI con INCREMENT score ≥8 punti

INCREMENT score:

Sepsi severa o shock settico:	5 punti
PITT score ≥6:	4 punti
Charlson index ≥2:	3 punti
Focolaio infettivo NON UTI o vie biliari:	3 punti

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doi:10.1093/jac/dky027

Journal of Antimicrobial Chemotherapy

Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/ Healthcare Infection Society/British Infection Association Joint Working Party†

Peter M. Hawkey[1]*, Roderic E. Warren[2], David M. Livermore[3], Cliodna A. M. McNulty[4], David A. Enoch[5], Jonathan A. Otter[6] and A. Peter R. Wilson[7]

AMIKACINA	Uso esperto con nomogrammi e TDM per ridurre la nefrotossicità
CEFTAZIDIME-AVIBACTAM	Uso in monoterapia o in associazione per CRE non MBL
FOSFOMICINA	Utile nelle UTI da CRE
GENTAMICINA	Uso in combinazione per UTI, IAI e BSI se ceppi sensibili a Genta, resistenti a Colistina e meropenem; rischio di nefro e ototossicità insieme ad altri farmaci nefrotossici
CARBAPENEMICI	Utile la MIC puntuale; per MIC tra 8 e 64 considera l'infusione continua. Aggiungere sempre se cefta/avi o merop/vaborbactam non possono essere utilizzati e se gli altri accompanying penetrano male
COLISTINA	Uso in associazione con aminoglicosidi o tigeciclina se meropenem con MIC≥32 mg/L. Riconsiderare l'uso per la SDD (cruciale non «sovrautilizzare» il farmaco). Uso di colistina aerosol
TIGECICLINA	Uso nelle infezioni dei tessuti molli e IAI; considerare dosaggio doppio nei pazienti critici

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Pipeline: beta-lattamici

	Company	CRE activity	MDR *Ps aerug* activity	MDR *Acinetobacter* activity	Key microbiologic features
Cefepime/zidebactam	Wockhardt	✓	✓	✓	+ AmpC, ESBL, KPC, OXA, MBL
WCK-5153	Wockhardt	NA	✓	✓	+ OXA-23, MBL
Meropenem/nacubactam	Roche	✓	✓		+ AmpC, ESBL, KPC, OXA
Cefepime/AAI101	Allecra	✓			+ AmpC, ESBL, KPC, OXA
VNRX5133	VenatoRx	NA	NA	NA	+ AmpC, ESBL, KPC, OXA, MBL
Aztreonam/avibactam	Pfizer	✓			+ AmpC, ESBL, KPC, OXA, MBL
Ceftaroline/avibactam	Pfizer	✓			+ AmpC, ESBL, KPC
Cefiderocol	Shionogi	✓	✓	✓	+ AmpC, ESBL, KPC, OXA, MBL
Imipenem/Relebactam	Merck	✓	✓		+ AmpC, ESBL, KPC
Meropenem/Vaborbactam	Melinta	✓			+ AmpC, ESBL, KPC

Pipeline: non beta-lattamici

	Company	CRE activity	MDR *Ps aerug* activity	MDR *Acinetobacter* activity
Murepavadin	Polyphor		✓	
Finafloxacin	MerLion	✓		✓
Eravacyclin	Tetraphase	✓		✓
Omadacycline	Paratek	✓		✓
Plazomicin	Achaogen	✓	✓	✓
Delafloxacin	Melinta	✓		✓

PLOS ONE

RESEARCH ARTICLE

Carbapenem-resistant Enterobacteriaceae colonization (CRE) and subsequent risk of infection and 90-day mortality in critically ill patients, an observational study

Thomas Howe McConville[1], Sean Berger Sullivan[1], Angela Gomez-Simmonds[1], Susan Whittier[2], Anne-Catrin Uhlemann[1]*

1 Department of Medicine, Division of Infectious Diseases, Columbia University Medical Center, New York, New York, United States of America, **2** Department of Pathology and Cell Biology, Clinical Microbiology Laboratory, Columbia University Medical Center, New York, New York, United States of America

Il 50% dei pz colonizzati da CRE ha sviluppato un'infezione da CRE nei 30 gg successivi

Table 2. Predictors of CRE infection within 30 days of intensive care unit admission.

Variable n (%)	No infection (n = 312)	Infection (n = 26)	Univariable p-value	Adjusted OR (95% CI)	Multivariable p-value
Within the previous 6 months					
Hospitalization	151 (48%)	24 (92%)	<0.0001	6.6 (1.3, 34.3)	0.03
Endoscopies					
EGD or colonoscopy	42 (13%)	11 (42%)	0.0006	3.7 (1.2, 11.1)	0.02
ERCP or EUS	6 (2%)	2 (8%)	0.1		
Antibiotic use	241 (77%)	25 (96%)	0.02	1.1 (0.1, 1.5)	0.9
Previous Ceph-R- or CRE infection			<0.0001		0.2*
No previous Ceph-R or CRE infection	270 (87%)	10 (38%)		REF	
Previous Ceph-R infection	31 (10%)	4 (15%)		2.1 (0.5, 9.6)	0.3
Previous CRE infection	11 (4%)	12 (46%)		3.5 (0.8, 14.8)	0.08
Colonization Resistance Phenotype			<0.0001		0.0003*
Non-colonized	237 (76%)	7 (27%)		REF	
Ceph-R colonized	56 (18%)	2 (8%)		0.5 (0.1, 3.3)	0.5
CRE colonized	19 (6%)	17 (65%)		10.8 (2.8, 41.9)	0.0006

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EPIDEMIOLOGY AND SURVEILLANCE

A Systematic Review and Meta-analyses of the Clinical Epidemiology of Carbapenem-Resistant *Enterobacteriaceae*

Karlijn van Loon,[a] Anne F. Voor in 't holt,[a] Margreet C. Vos[a]

[a]Department of Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands

INTERVENTI PIU' EFFICACI PER IMPEDIRE LA DIFFUSIONE DEI CRE:

- ✓Isolamento da contatto
- ✓Patient cohorting
- ✓Sorveglianza attiva

World Health Organization

Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities

3.1 Recommendation 1: Implementation of multimodal infection prevention and control strategies

The panel recommends that multimodal IPC strategies should be implemented to prevent and control CRE-CRAB-CRPsA infection or colonization and that these should consist of at least the following:

- hand hygiene
- surveillance (particularly for CRE)
- contact precautions
- patient isolation (single room isolation or cohorting)
- environmental cleaning

(Strong recommendation, very low to low quality of evidence)

3.2 Recommendation 2: Importance of hand hygiene compliance for the control of CRE-CRAB-CRPsA

The panel recommends that hand hygiene best practices according to the *WHO guidelines on hand hygiene in health care* should be implemented *(6)*.

(Strong recommendation, very low quality of evidence)

3.3 Recommendation 3: Surveillance of CRE-CRAB-CRPsA infection and surveillance cultures for asymptomatic CRE colonization

The panel recommends that:

a) **surveillance of CRE-CRAB-CRPsA infection(s) should be performed, and**

b) **surveillance cultures for asymptomatic CRE colonization should also be performed, guided by local epidemiology and risk assessment. Populations to be considered for such surveillance include patients with previous CRE colonization, patient contacts of CRE colonized or infected patients and patients with a history of recent hospitalization in endemic CRE settings.**

(Strong recommendation, very low quality of evidence)

3.4 Recommendation 4: Contact precautions

The panel recommends that contact precautions should be implemented when providing care for patients colonized or infected with CRE-CRAB-CRPsA.

(Strong recommendation, very low to low quality of evidence)

3.5 Recommendation 5: Patient isolation

The panel recommends that patients colonized or infected with CRE-CRAB-CRPsA should be physically separated from non-colonized or non-infected patients using
a) single room isolation; or
b) cohorting patients with the same resistant pathogen.

(Strong recommendation, very low to low quality of evidence)

3.6 Recommendation 6: Environmental cleaning

The panel recommends that compliance with environmental cleaning protocols of the immediate surrounding area (that is, the "patient zone") of patients colonized or infected with CRE-CRAB-CRPsA should be ensured.

(Strong recommendation, very low quality of evidence)

3.7 Recommendation 7: Surveillance cultures of the environment for CRE-CRAB-CRPsA colonization/contamination

The panel recommends that surveillance cultures of the environment for CRE-CRAB-CRPsA may be considered when epidemiologically indicated.

(Conditional recommendation, very low quality of evidence)

3.8 Recommendation 8: Monitoring, auditing and feeback

The panel recommends monitoring, auditing of the implementation of multimodal strategies and feedback of results to health care workers and decision-makers.

(Strong recommendation, very low to low quality of evidence)

PLOS ONE

RESEARCH ARTICLE

Carbapenem-resistant Gram-negative pathogens in a German university medical center: Prevalence, clinical implications and the role of novel β-lactam/β-lactamase inhibitor combinations

Juri Katchanov[1], Lucia Asar[2], Eva-Maria Klupp[2], Anna Both[2], Camilla Rothe[3], Christina König[1,4], Holger Rohde[2], Stefan Kluge[1], Florian P. Maurer[2]*

Table 3. Distribution, initiation of treatment and in-hospital mortality of patients colonized or infected with carbapenem-resistant MDR-GNB.

Sample category	Likelyhood for infection	n of pts (% total)	treated for infection, n of pts (%)	in-hospital mortality (%)
blood cultures	very high	11 (9,2%)	10 (90,9%)	81,8%
intraoperative swabs, tissue biopsies	high	7 (5,9%)	5 (71,4%)	71,4%
respiratory samples (TS, BAL, and sputum)	equivocal	58 (48,7%)	28 (48,3%)	27,6%
superficial swabs (wound swabs, ulcus swabs)	low	9 (7,6%)	0 (0,0%)	0,0%
routine screening swabs (nasal, rectal)	very low	34 (28,6%)	7 (20,6%)	29,4%

Patients were stratified by the sample category from which carbapenem-resistant MDR-GNB were obtained. Patients in whom MDR-GNB were isolated from more than one specimen were counted once in the category with the highest likelihood for infection. Abbreviations: n of pts, number of patients; TS, tracheal secretion; BAL, bronchoalveolar lavage

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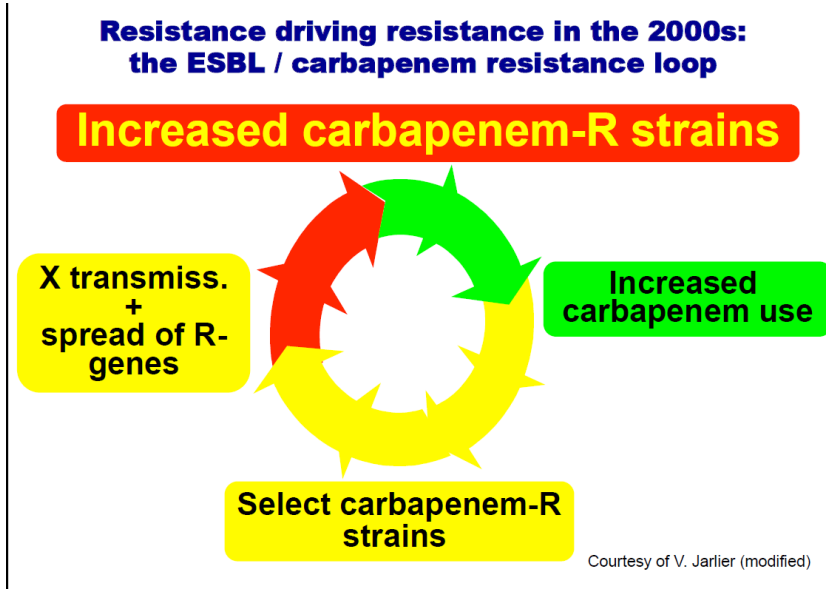
ALTRE QUESTIONI APERTE

- Profilassi chirurgica nei pazienti colonizzati con CRE ?
- I dati del trial MERINO potranno influenzare ulteriormente il consumo di carbapenemi e l'aumento dei ceppi CRE?



GRAZIE DELL'ATTENZIONE !

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