

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

Department of Public Health and Infectious Diseases, Policlinico Umberto I, University of Rome Sapienza, Rome, Italy^a; Department of Emergency Medicine, Policlinico

Umberto I, University of Rome Sapienza, Rome, Italy^b; Department of Bio-Medical Sciences, University of Catania, Catania, Italy^c

Severe infections caused by carbapenemase-producing *Klebsiella pneumoniae* are becoming a significant problem worldwide and are associated with high morbidity and mortality rates (1–3). Recently, treatments based on therapies with combinations of colistin, tigecycline, meropenem, fosfomycin, and/or aminoglycoside have been suggested (4–6). However, the emergence of strains resistant to almost all of the antibiotics listed above has further complicated the possibility of treating these infections (7–9).

A 65-year-old male was admitted to the Neurosurgical Intensive Care Unit of Azienda Policlinico Umberto I in Rome for treatment of cerebral hemorrhage and hydrocephalus that occurred 3 days after a surgical excision of a subependymoma. The patient was intubated and mechanically ventilated.

On day 25 of admission, the clinical course was complicated by the development of a bacteremia with severe sepsis due to *Enterobacter aerogenes* that was successfully treated with meropenem (1 g every 8 h [q8h]). On day 43, the patient once again developed a high-grade fever with multiple pulmonary bilateral infiltrates. Blood cultures and semiquantitative cultures of endotracheal aspirates yielded colistin/tigecycline-resistant, multidrug-resistant (MDR) *K. pneumoniae* isolates according to the bioMérieux Vitek-2 automated system.

Despite the antibiotic treatment with colistin (loading dose of 9 MU followed by 4.5 MU q12h), meropenem (2 g q8h), and rifampin (300 mg q8h) for 6 days and afterward with colistin plus fosfomycin (3 g q8h) for 5 days, high fever and bacteremia persisted, with an increase of procalcitonin levels (to 140 ng/ml), development of multiple-organ-dysfunction syndrome (total bilirubin, 14.9 mg/dl; creatinine, 3 mg/dl; platelets, 28,000/l, PaO₂/FiO₂ 300) and the need for inotropic drug support. A subsequent laboratory study, in which both broth microdilution (BMD) analysis and an Etest were performed, confirmed that these isolates (4 isolates collected since day 47 of hospitalization from 3 blood cultures and 1 endotracheal aspirate) were resistant to ertapenem, meropenem, imipenem, doripenem, amikacin, colistin, and fosfomycin but evidenced that they were susceptible to tigecycline with both methods, confirming the overestimation of the MIC for this drug if performed with the Vitek2 system (Table 1) (6, 10). The same clinical isolates, genotyped by pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST), belonged to the same clone and were sequence type (ST)

512. PCR detection showed that all isolates harbored the *bla*_{KPCsub} gene (11).

On day 52, therapy was modified to ertapenem (500 mg q24h) plus doripenem (250 mg q8h by a 4-h-extended infusion) according to the initial values of creatinine clearance. Tigecycline therapy

TABLE 1 Antibiotic susceptibility comparison by Vitek 2, broth microdilution, and Etest methods against 4 *K. pneumoniae* isolates^a

Isolate no. (day of hospitalization)	Specimen	Antibiotic	MIC (mg/liter) ^b		
			Vitek 2	Etest	BMD
1 (48)	Endotracheal aspirate	IPM	16	32	32
		MEM	16	32	64
		ERTA	8	32	256
		DOR	n.t	n.t	64
		AK	64	48	32
		COL	16	2	32
		FOSFO	128	32	64
		TGC	8	0.38	0.5
		2 (48)	Blood	IPM	16
MEM	16			32	64
ERTA	8			32	512
DOR	n.t			n.t	32
AK	64			48	32
COL	16			4	16
FOSFO	128			64	128
TGC	8			1	0.5
3 (53)	Blood			IPM	16
		MEM	16	32	64
		ERTA	8	32	64

		DOR	n.t	n.t	64
		AK	64	48	32
		COL	16	6	16
		FOSFO	128	32	64
		TGC	8	0.38	0.5
4 (59)	Blood	IPM	16	32	32
		MEM	16	32	64
		ERTA	8	32	512
		DOR	n.t	n.t	64
		AK	64	64	32
		COL	16	4	16
		FOSFO	128	32	64
		TGC	8	0.75	0.5

^a Abbreviations: BMD, broth microdilution; IPM, imipenem; MEM, meropenem; ERTA, ertapenem; DOR, doripenem; AK, amikacin; COL, colistin; FOSFO, fosfomycin; TGC, tigecycline; n.t, not tested. ^b Data represent 2013 EUCAST breakpoints.

Published ahead of print 9 April 2013

Address correspondence to Mario Venditti, mario.venditti@uniroma1.it or Marco Falcone, marcofalco@libero.it.

Copyright © 2013, American Society for Microbiology. All Rights Reserved.

doi:10.1128/AAC.00188-13

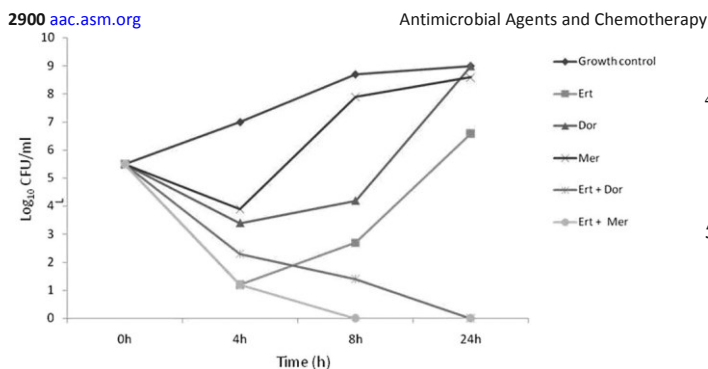


FIG1 Time-kill curves for *K. pneumoniae* with ertapenem (Ert) at 1 MIC (512 mg/liter), doripenem (Dor) at 1 MIC (64 mg/liter), meropenem (Mer) at 1 MIC (64 mg/liter), and the combinations of ertapenem plus doripenem at 1 MIC and ertapenem plus meropenem at 1 MIC.

was not considered because, at the moment when we choose therapy, the only available data were those obtained with the Vitek-2 automated system, which showed tigecycline-resistant isolates. The patient remained febrile for a further 4 days, whereas the bacteremia cleared after 8 days. Subsequently, inotropic

support was discontinued, and the PaO₂/FiO₂ ratio and platelet count values returned gradually to normal within 2 weeks, creatinine and total bilirubin values to normal in 3 weeks, and the procacilatin value to normal in 4 weeks. With the improvement of renal function, ertapenem was administered at a dose of 1,000 mg q24h and doripenem at a dose of 500 mg q8h (day 67) up to 1,000 g q8h (day73). Eventually, the patient completed a 4-week dual-carbapenem treatment course. No relapse was observed after 1 month of follow-up after discontinuation of the antibiotics.

The activity of the carbapenem combination was also confirmed *in vitro* with the striking synergy that was observed in the studies of the killing curves. In fact, in these experiments, the combination of ertapenem plus doripenem at 1 MIC was strongly synergic after 4 h, achieving 99.9% killing, as was ertapenem plus meropenem, maintaining this behavior until 24 h. The value for ertapenem alone showed an increase of 1 log after 24h, while those for doripenem and meropenem alone showed an increase of 3 log (Fig. 1).

Our case report on the result obtained *in vitro* and *in vivo* with a KPC-3-producing *K. pneumoniae* seems to corroborate experiments performed by Bulik et al. (12), who recently postulated that the enhanced efficacy of this dual-carbapenem therapy against KPC-2-producing *K. pneumoniae* may be related to the KPC enzyme's preferential affinity for ertapenem.

ACKNOWLEDGMENTS

G.C. and M.F. contributed equally to this article.

We declare that we have no conflicts of interest.

Letter to the Editor

REFERENCES

- Orsi GB, Falcone M, Venditti M. 2011. Surveillance and management of multidrug-resistant microorganisms. *Expert Rev. Anti Infect. Ther.* 9:653–679.
- Orsi GB, Bencardino A, Vena A, Carattoli A, Venditti C, Falcone M, Giordano A, Venditti M. 2013. Patient risk factors for outer membrane permeability and KPC-producing carbapenem-resistant *Klebsiella pneumoniae* isolation: results of a double case-control study. *Infection* 41:61–67.
- Orsi GB, Garcia-Fernandez A, Giordano A, Venditti C, Bencardino A, Gianfreda R, Falcone M, Carattoli A, Venditti M. 2011. Risk factors for and clinical significance of ertapenem-resistant *Klebsiella pneumoniae* in hospitalised patients. *J. Hosp. Infect.* 78:54–58.
- Pournaras S, Vrioni G, Neou E, Dendrinos J, Dimitroulia E, Poulou A, Tsakris A. 2011. Activity of tigecycline alone and in combination with colistin and meropenem against *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* strains by time-kill assay. *Int. J. Antimicrob. Agents* 37:244–247.
- Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, Spanu T, Ambretti S, Ginocchio F, Cristini F, Losito AR, Tedeschi S, Cauda R, Bassetti M. 2012. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. *Clin. Infect. Dis.* 55:943–950.
- Sbrana F, Malacarne P, Viaggi B, Costanzo S, Leonetti P, Leonildi A, Casini B, Tascini C, Menichetti F. 2013. Carbapenem-sparing antibiotic regimens for infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* in intensive care unit. *Clin. Infect. Dis.* 56:697–700.
- Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M, Venditti M, Bordi E, Capozzi D, Balice MP, Tarasi A, Parisi G, Lappa A, Carattoli A, Petrosillo N; on behalf of the SEERBIO-GRAB network. 2013. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae*

- infection accounts for an excess of mortality. *Clin. Microbiol. Infect.* **19**:E23–E30.
8. **Karageorgopoulos DE, Wang R, Yu XH, Falagas ME.** 2012. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. *J. Antimicrob. Chemother.* **67**: 255–268.
 9. **Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL.** 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin. Microbiol. Infect.* **18**: 268–281.
 10. **European Committee on Antimicrobial Susceptibility Testing.** 2013. Breakpoint tables for interpretation of MICs and zone diameters, version 3.0. EUCAST, Växjö, Sweden.
 11. **Mezzatesta ML, Gona F, Caio C, Petrolito V, Sciortino D, Sciacca A, Santangelo C, Stefani S.** 2011. Outbreak of KPC-3-producing, and colistin resistant, *Klebsiella pneumoniae* infections in two Sicilian hospitals. *Clin. Microbiol. Infect.* **17**:1444–1447.
 12. **Bulik CC, Nicolau DP.** 2011. Double-carbapenem therapy for carbapenemase-producing *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **55**:3002–3004.