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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 ofcolistin,tigecycline,meropenem,fosfomycin,and/oraminoglycoside 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 IntensiveCareUnitofAziendaPoliclinicoUmbertoIinRomefortreatment 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 *Enterobacteraerogenes*thatwassuccessfullytreatedwithmeropenem(1g 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.

Despitetheantibiotictreatmentwithcolistin(loadingdoseof9 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, PaO^2/FiO^2 300) 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_{KPC}sub gene (11).

On day 52, therapy was modified to ertapenem (500 mg q24h) plus doripenem (250 mg q8h by a 4-h-extended infusion) accordingtotheinitialvaluesofcreatinineclearance.Tigecyclinether apy

TABLE1 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	32	32
		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	32	32
		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.

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

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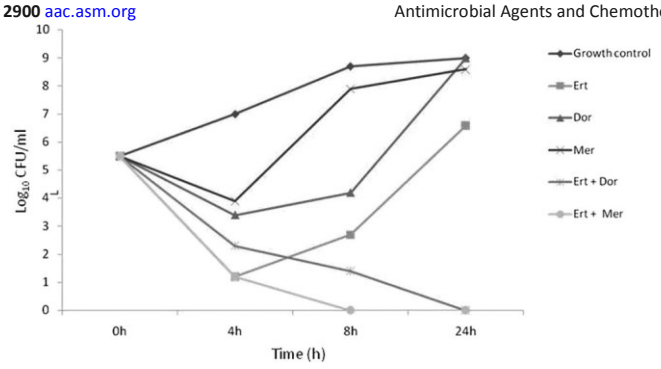

FIG1 Time-kill curves for *K. pneumoniae* with ertapenem (Ert) at 1 MIC (512 mg/liter), doripenem (Dor) at 1 MIC (64 mg/liter), meropenem (Mer) at 1 MIC (64 mg/liter), and the combinations of ertapenem plus doripenem at 1 MIC and ertapenem plus meropenem at 1 MIC.

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 procaciltonin 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,thepatientcompleteda4-weekdual-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,achieving99.9%killing,aswasertapenemplusmeropenem,mainta ining this behavior until 24 h. The value for ertapenem alone showedanincreaseof1logafter24h,whilethosefordoripenemand 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.

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We declare that we have no conflicts of interest.

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