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Successful Treatment with Imipenem/Cilastatin/ Relebactam of a Polymicrobial Bacteremia due to Meropenem/Vaborbactam-Resistant KPC-Kp and Enterococcus Faecalis

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To the editor.

Infections caused by carbapenemase-producing Klebsiella pneumoniae (KPC-Kp)represent a major global public health threat, associated with high mortality rates and limited therapeutic options.[1,2] In Italy, recent surveillance data from the Istituto Superiore di Sanità (ISS) confirm that, while some surveillance data suggest a slight decrease in carbapenem resistance rates, KPC-Kp remains endemic, with a significant impact on clinical outcomes.[15] While novel β-lactam/β-lactamase inhibitor combinations (BL/BLI) like meropenem/vaborbactam (M/V) have improved management, the emergence of resistance, often mediated by porin mutations or increased gene copy numbers, necessitates the use of alternative agents.[2,4,7] Imipenem/cilastatin/relebactam (IMI/REL) combines a carbapenem with a potent class A/C β-lactamase inhibitor (relebactam), which restores imipenem's activity against many carbapenem-resistant strains.[3-6]

Case Presentation. An 80-year-old male, residing in a long-term care facility with advanced Parkinson's disease and complete loss of autonomy, presented to the Emergency Department with fever and tachycardia. His medical history was significant for chronic bed-bound status, hypertensive heart disease, multifactorial anemia, and previous episodes of sepsis. Upon admission, laboratory tests revealed marked leukocytosis (WBC 45,510/µL), elevated CRP (10.07 mg/dL), and a critical procalcitonin level (88.24 ng/mL). Chest X-ray showed an inflammatory consolidation in the left lower lobe. The patient was admitted to the Internal Medicine department and, based on preliminary blood cultures identifying Klebsiella pneumoniae, treatment with meropenem/vaborbactam and vancomycin was started.

Final blood cultures results identified a polymicrobial bacteremia involving Enterococcus faecalis (susceptible to ampicillin and vancomycin) and KPC-Kp. Notably, the KPC-Kp isolate was resistant to meropenem/vaborbactam (MIC>8$\mu g/mL$) but susceptible to IMI/REL (MIC≤2$\mu g/mL$) (**Figure 1**).

Following the antibiogram, the regimen was switched to IMI/REL (500/500/250 mg every 6 hours). The patient experienced rapid clinical and laboratory improvement without adverse effects. Blood cultures repeated at 72 hours showed no growth**.** After 7 days of treatment, white blood cell count normalised (6,320/µL), and procalcitonin increased to 1.56 ng/mL. Echocardiography ruled out endocarditis, and the patient was discharged in improved clinical condition.

Discussion. To our knowledge, this is the first clinical report of KPC-producing K. pneumoniae bacteremia resistant to meropenem/vaborbactam and concurrently susceptible to imipenem/cilastatin/relebactam, with documented microbiological clearance and favorable outcome. Evidence of this divergent resistance pattern has so far been largely limited to in vitro studies and pharmacodynamic models, without in vivo confirmation.[2,4,7-9]

In vitro and genomic data indicate that meropenem/vaborbactam resistance is often linked to alterations in the OmpK35 and OmpK36 porins (including the GD134-135 insertion), which restrict carbapenem uptake.[2,5–7] Relebactam appears to be less affected by these porin changes than vaborbactam, which may contribute to the divergent susceptibilities observed in some KPC-producing K. pneumoniae isolates.[5,6,9] In our case, these mechanisms were not confirmed at the molecular level and remain a hypothesis based on the literature.

Recent Italian and US surveys confirm emerging resistance to novel BL/BLI, while showing that susceptibility is not always cross-reactive.[2,6,9] Our case illustrates the successful use of IMI/REL as rescue therapy in an elderly, high-risk patient — a group often

IDENTIFICAZIONE- 1 - Klebsiella pneumoniae

IDENTIFICAZIONE- 2 - Enterococcus faecalis

ANTIBIOGRAMMA	- 1 -	MIC(ug/ml)	- 2 -	MIC(ug/ml)
Amoxi-ac.clav OS (altre indicazioni)	R	>=64		
Amoxi-ac.clav OS IVU non complicate	R	>=64		
Amoxi-ac.clav terapia IV	R	>=64		
Amoxicillina/A.CLAV.			S	<=2
Ampicillina	R	>=32	S	<=2
Ampicillina/sulbactam	R	>=32	S	<=2
Aztreonam	R	>=64		
Cefepime	R	>=32		
Ceftazidime	R	>=64		
Ceftolozane/Tazobactam	R	>=32		
Cefuroxime	R	>=64		
Ciprofloxacina (meningite)	R	>=4		
Ciprofloxacina (altre indicazioni)	R	>=4		
Colistina	S	0.5		
Ertapenem	R	>=8		
Esbl	-	Neg		
Gentamicina	R	>=16		
Imipenem	R	>=16	I	2
Imipenem/Relebactam	S	1		
Kanamicina alta conc			R	SYN-R
Levofloxacin	R	>=8		
Linezolid			S	2
Meropenem (altre indicazioni)	R	>=16		
Meropenem (meningite)	R	>=16		
Meropenem/Vaborbactam	R	32		
Moxifloxacina	R	>=8		
Piperacillina/tazobactam	R	>=128		
Streptomicin alta c.			R	SYN-R
Teicoplanina			S	<=0.5
Vancomicina			S	1
Cefotaxime (meningite)	R	>=64		
Cefotaxime (altre indicazioni)	R	>=64		
Ceftriaxone (altre indicazioni)	R	>=64		
Ceftriaxone (meningite)	R	>=64		

Figure 1. Antibiogram of the KPC-producing Klebsiella pneumoniae and E. Faecalis strains isolated from blood. S = Sensitive to standard dosage. I = Sensitive To Increased Exposure. R = Resistant. Sensitivity assays and clinical breakpoints are interpreted according to EUCAST criteria. Specifically, the susceptibility breakpoint for IMI/REL is ≤ 2 mg/L and for M/V is ≤ 8 mg/L. Platform used is VITEK 2.

underrepresented in randomized trials.[3-4,12-13] Consistent with our findings, real-world data, including an Italian series by Gaibani et al. and larger US cohorts, report clinical success rates around 70% with IMI/REL, supporting its role even in severe bacteremia and polymicrobial infections.[10,13-15]

Conclusions. This case highlights the central role of antimicrobial stewardship in managing infections caused by multidrug-resistant organisms. Microbiology-driven susceptibility testing of novel β-lactam/β-lactamase inhibitor combinations is essential, as resistance to one agent does not imply cross-resistance.

Targeted use of imipenem/cilastatin/relebactam led to clinical and microbiological cure while avoiding unnecessary therapeutic escalation, reinforcing stewardship as a key strategy to preserve last-line antibiotics and optimize patient outcomes.

Ethical approval. Written informed consent for publication was obtained from the patient's legally authorized representative in accordance with institutional policy.

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