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LETTER TO THE EDITOR

Ceftazidime-avibactam for gram-negative multidrug-resistant bacteria in hematological patients: a single-center experience

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Dear Editor,

We have read with interest the paper conducted by the SEIFEM group, concerning the severe problem of multidrug-resistant (MDR) infection in the hematological setting. In a multicentric prospective observational study, Cattaneo and colleagues recorded a colonization rate of 6.5% at admission, with a 16% probability of MDR-related bloodstream infection (BSI), particularly in neutropenic patients. Among them, a carbapenem-resistant gram-negative bacteria was responsible for the 59% of the colonized patients [1].

Over the last years, an increased rate of carbapenem-resistant *Enterobacteriaceae* (CRE) and MDR *Pseudomonas aeruginosa* was registered. [2].

Recently, a combination of ceftazidime and avibactam was approved against MDR gram-negative bacteria. Various clinical studies in which ceftazidime/avibactam has been used for CRE infection showed an overall response rate ranging from 45 to 74% [3].

Castòn et al. [4] first reported results on ceftazidime/avibactam in hematological patients with CRE bacteremia ($N = 31$). They compared 8 patients receiving ceftazidime/avibactam plus other agents with 23 patients who had received others antimicrobial treatment. The 30-days mortality was 25% in the ceftazidime/avibactam group as compared to 52% for the others, with a response rate to treatment of 75% and 35%, respectively.

The international, randomized, phase 3 study (REPRISE; NCT01644643) [5] reported results on efficacy of ceftazidime/avibactam in patients with MRD gram-negative pathogen infections. The overall microbiological response rate was of approximatively 80% for both *Klebsiella pneumoniae* and *P. aeruginosa*. Favorable microbiological response was observed also for those patients with ceftazidime/avibactam provisionally resistant strains (MIC > 8 mg/L).

Here, we report the results of our single-center experience with ceftazidime/avibactam in three hematological patients with MDR gram-negative bacteremia. Strains were identified to the species level with matrix-assisted laser desorption ionization-time-of-flight (MALDITOF) mass spectrometry (MS) (BrukerDaltonik or Vitek MS; bioMérieux, Marcy l'Etoile, France). The antibiotic susceptibility profiling of isolates was carried out with the Vitek 2 system (bioMérieux). Results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints [6]. Detailed patients and pathogen characteristics are reported in Table 1. Ethical Committee approval and informed written consent from each patient was obtained for the compassionate use of Zavicefta® [7], provided free of charge by Clinigen Group plc. All patients had severe persistent neutropenia (< 0.5×10^9/L) and persistent septic signs, despite empirical therapy. According to antibiotic susceptibility, ceftazidime/avibactam was added to the current antibiotics combination after a median of 4 days (range, 4 to 6) at the recommended dose of 2.5 g tid. Median duration of the treatment was of 15 days (range, 12 to 16). After that, patients n.1 and n.3 obtained a clinical and microbiological response, whereas patient n.2 died after 12 days of treatment because of respiratory failure and massive bleeding. In the two survived patients, clinical response was obtained in few days after ceftazidime/avibactam introduction, resulting in a progressive neutrophils count recovery and microbiological response. Unfortunately, in patient n.2, comorbidities, age, deep immunosuppression early after allogeneic transplantation, and septic shock at clinical presentation surely negatively affected the unfavorable outcome. Therefore,

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Table 1 Detailed patients and infections description

	Patient 1	Patient 2	Patient 3
Age	52	69	61
Sex	Male	Male	Male
Other infection (last 30 days)	KPC-Kp (perineal abscess)	*E. faecium* (blood) MRSA (blood)	*E. faecalis* (urine) *P. aeruginosa* MDR (glans ulcer)
Comorbidities	Acute myeloid leukemia (responsive disease) Consolidation cycle of chemotherapy CVC	COPD Myelodysplastic syndrome (complete remission after reinduction) Allogeneic stem cell transplant Immunosuppression (CSA and MFA) CVC Foley catheter	Valvulopathy Ocular melanoma Acute myeloid leukemia at diagnosis Induction chemotherapy Foley catheter
Previous hospitalization	Yes (last 3 months)	No	No
Days of neutropenia (< 0.5x10^9/L) before infection	9	4	16
Charlson index	3	3	3
Pathogen BSI	*K. pneumoniae*	*K. pneumoniae*	*P. aeruginosa*
Days from admission to BSI	5	15	17
First colonized sites	Anal tract	Anal tract	Scrotal ulcer
Clinical presentation	Sepsis	Septic shock	Sepsis
Sensitivity (MIC mg/L)	Amikacin (≥ 64) R Amoxicillin/clavulanate (≥ 32) R Ampicillin (≥ 32) R Cefepime (≥ 64) R Cefotaxime (≥ 64) R Ceftazidime (≥ 64) R **Ceftazidime/avibactam (≤ 1) S** Ciprofloxacin (≥ 4) R Colistin (4) R **Fosfomycin (32) S** **Gentamicin (1) S** Imipenem (≥ 16) R Meropenem (≥ 16) R Piperacillin/tazobactam (≥ 128) R **Tigecycline (0.5) S**	Amikacin (≥ 64) R Amoxicillin/clavulanate (≥ 32) R Ampicillin (≥ 32) R Cefepime (≥ 64) R Cefotaxime (≥ 64) R Ceftazidime (≥ 64) R **Ceftazidime/avibactam (2) S** Ciprofloxacin (≥ 4) R **Colistin (1) S** **Gentamicin (1) S** Imipenem (≥ 16) R Meropenem (≥ 16) R Piperacillin/tazobactam (≥ 128) R **Tigecycline (0.5) S**	Amikacin (≥ 64) R Amoxicillin/clavulanate (≥ 32) R Ampicillin (≥ 32) R Cefepime (≥ 64) R Ceftazidime (≥ 64) R **Ceftazidime/avibactam (4) S** Ceftozolane/tazobactam (> 8) R Ciprofloxacin (≥ 4) R Colistin (4) R Gentamicin (≥ 16) R Imipenem (2) R Meropenem (46) R Piperacillin/tazobactam (32) R
Empirical treatment for BSI (based on antibiogram of colonizing pathogen)	Meropenem 2 g tid Tigecycline 100 mg bid Colistin 4.5 MU bid	Meropenem 2 g tid Tigecycline 100 mg bid Colistin 4.5 MU bid	Meropenem 2 g tid Tigecycline 100 mg bid Colistin 4.5 MU bid
Duration of empirical treatment	6 days	4 days	4 days
Targeted treatment for BSI	Meropenem 2 g tid Tigecycline 100 mg bid Colistin 4.5MU bid Ceftazidime/avibactam 2.5 g tid	Ceftazidime/avibactam 2.5 g tid Tigecycline 100 mg bid Colistin 4.5 MU bid	Ceftazidime/avibactam 2.5 g tid Meropenem 2 g tid Tigecycline 100 mg bid
Duration of targeted treatment	15 days	12 days	16 days
Duration of neutropenia (days)	22	20 (died neutropenic)	24
Outcome	Infection resolved	Fever resolved	Infection resolved
Cause of 30-days death	–	Massive bleeding and respiratory distress	–

Bold entries identified antibotics for which a sensitivity was documented for each isolated pathogen

Abbreviations: *MRSA*, methicillin-resistant *Staphylococcus aureus*; *COPD*, chronic obstructive pulmonary disease; *CVC*, central venous catherer; *CSA*, cyclosporine A; *MMF*, mycophenolate mofetil; *MDR*, multidrug resistant; *BSI*, bloodstream infection. Sepsis: temperature > 38 °C, tachycardia, chills, hypoxia; septic shock: temperature > 38 °C, tachycardia, respiratory distress, hypotension, urinary impairment, hepatic injury; *S*, sensitive; *R*, resistant; *I*, intermediate.

even if our study cohort is too small to allow some conclusions, we believe that ceftazidime/avibactam might improve the outcome in hematological patients with MDR bacteria BSI.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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