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Effectiveness of ceftazidime/avibactam as salvage therapy for treatment of infections due to OXA-48 carbapenemase-producing Enterobacteriaceae

Adrian Sousa[1,2], María Teresa Pérez-Rodríguez[1,2]*, Adriana Soto[1], Lorena Rodríguez[1], Antonio Pérez-Landeiro[3], Lucia Martínez-Lamas[4], Andrés Nodar[1,2] and Manuel Crespo[1,2]

[1]Infectious Diseases Unit-Internal Medicine Department, Hospital Álvaro Cunqueiro, Complejo Hospitalario Universitario de Vigo, Vigo, Spain; [2]Instituto de Investigación Sanitaria Galicia Sur (IIS Galicia Sur), Hospital Álvaro Cunqueiro Bloque técnico, Estrada Clara Campoamor 341, 36312 Vigo (Pontevedra), Spain; [3]Pharmacy Department, Hospital Álvaro Cunqueiro, Complejo Hospitalario Universitario de Vigo, Vigo, Spain; [4]Microbiology Department, Hospital Álvaro Cunqueiro, Complejo Hospitalario Universitario de Vigo, Vigo, Spain

*Corresponding author. Infectious Diseases Unit, Internal Medicine Department, Hospital Álvaro Cunqueiro-Complejo Hospitalario Universitario de Vigo, IIS Galicia Sur, Estrada Clara Campoamor 341, 36212 Vigo (Pontevedra), Spain. Tel: +34 666 091 418; E-mail: perezrodriguezmt@gmail.com

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Background: Experience in real clinical practice with ceftazidime/avibactam is limited, and there are even fewer data on infections due to OXA-48-producing Enterobacteriaceae.

Methods: We designed an observational study of a prospectively collected cohort of adult patients receiving ceftazidime/avibactam in our centre. Only the first treatment course of each patient was analysed. Efficacy and safety were evaluated as 14 and 30 day mortality, recurrence rate at 90 days, resistance development and occurrence of adverse effects.

Results: Fifty-seven patients were treated with ceftazidime/avibactam. The median age was 64 years (range 26–86), 77% were male and the median Charlson index was 3. The most frequent sources of infection were intra-abdominal (28%), followed by respiratory (26%) and urinary (25%). Thirty-one (54%) patients had a severe infection (defined as presence of sepsis or septic shock). Most patients received ceftazidime/avibactam as monotherapy (81%) and the median duration of treatment was 13 days. Mortality at 14 days was 14%. In multivariate analysis, the only mortality risk factor was INCREMENT-CPE score >7 (HR 11.7, 95% CI 4.2–20.6). There was no association between mortality and monotherapy with ceftazidime/avibactam. The recurrence rate at 90 days was 10%. Ceftazidime/avibactam resistance was not detected in any case and only two patients developed adverse events related to treatment.

Conclusions: Ceftazidime/avibactam shows promising results, even in monotherapy, for the treatment of patients with severe infections due to OXA-48-producing Enterobacteriaceae and limited therapeutic options. The emergence of resistance to ceftazidime/avibactam was not observed.

Introduction

In recent years there has been an increase in the incidence of infections caused by multiresistant microorganisms, mainly ESBL- and carbapenemase-producing organisms. These have become a serious public health and clinical problem, leading to higher mortality and poorer prognosis in patients infected with these microorganisms.[1,2] The development of new drugs is one of the main strategies to fight against infections due to these microorganisms.

Ceftazidime is a widely known third-generation cephalosporin active against Enterobacteriaceae and *Pseudomonas* spp. and is used in the hospital environment in combination with avibactam, a new synthetic inhibitor of β-lactamases with potent activity against class A (including ESBLs and KPC-type carbapenemases), class C and some class D β-lactamases (including OXA-48).[3] Ceftazidime/avibactam is not active against MBLs such as NDM, IMP and VIM.[3,4]

Some results obtained from *in vitro* studies showed high activity of ceftazidime/avibactam against Enterobacteriaceae and *Pseudomonas aeruginosa*. According to data reported by Castanheira *et al.*,[5] the susceptibility of Enterobacteriaceae to ceftazidime/avibactam was 99.9% among 20000 clinical isolates, and only 3 of 120 KPC-type carbapenemase-producing strains showed resistance to ceftazidime/avibactam. In another *in vitro*

study, by Sader *et al.*,[6] 67% of 393 strains of meropenem-resistant *P. aeruginosa* were susceptible to ceftazidime/avibactam (most of the non-susceptible isolates were MBL producers).

Phase III randomized clinical trials have evaluated the efficacy of ceftazidime/avibactam in the treatment of complicated urinary tract infections,[7,8] intra-abdominal infections[9] and nosocomial pneumonia.[10] Most of the available data on the effectiveness and safety of ceftazidime/avibactam in real clinical practice is obtained from observational studies and the information available is still limited. In addition, scarce information exists regarding the effectiveness of ceftazidime/avibactam monotherapy in high-risk patients, and the recently reported development of resistance during treatment is a further concern.[11–13]

The aim of our study was to analyse the effectiveness and safety of ceftazidime/avibactam for the treatment of infections due to carbapenemase-producing Enterobacteriaceae (CPE) in a cohort of patients treated in our centre during an epidemic outbreak of OXA-48-producing *Klebsiella pneumoniae*.

Methods

This was an observational study in which we retrospectively analysed the database of our Infectious Diseases Unit, the data having been collected in real time. This database includes all patients with CPE infections since the start of the outbreak situation in our institution. All patients treated with ceftazidime/avibactam (for at least 48 h) for any infection produced by OXA-48-producing CPE between 1 April 2016 and 31 December 2017 were included.

From the end of 2015, our hospital experienced an outbreak of infections due to OXA-48-type carbapenemase-producing *K. pneumoniae*. Starting on 1 April 2016, ceftazidime/avibactam was available in our centre for the treatment of patients with CPE infections that met one of these criteria: (i) poor clinical course with adequate antibiotic treatment (all patients with this criterion were initially treated with a combination therapy of double-dose extended-infusion carbapenem and colistin); (ii) contraindication or impossibility of use owing to unacceptable risk of toxicity associated with the use of other appropriate antibiotic options (for example, in patients with impaired renal function in which the initiation of colistin treatment posed a risk of increased nephrotoxicity); and (iii) toxicity of previous antibiotic treatment (e.g. neurotoxicity caused by carbapenem treatment or acute tubular necrosis due to colistin treatment).

Every patient was evaluated by a member of the Infectious Diseases Unit at the beginning of treatment and/or during the follow-up. Infections were defined according to the CDC criteria.[14] In patients who had had more than one episode treated with ceftazidime/avibactam only the first one was analysed.

Variables and definitions

The main outcome variable was 14 day all-cause mortality. Secondary outcomes were 30 day all-cause mortality, clinical cure and microbiological cure. The main safety outcomes were occurrence of adverse events and/or development of resistance during or after treatment. The main exposure of interest was antibiotic therapy with ceftazidime/avibactam either as monotherapy or in combination treatment.

Collected data included demographic characteristics, chronic underlying conditions, infection characteristics (severity, onset of infection, source of infection) and treatment characteristics (combination therapy, previously administered treatment, delay in initiation of ceftazidime/avibactam). The Charlson comorbidity index was determined at admission.[15] Source control was considered adequate if it was performed within 1 week of the diagnosis of infection (surgical procedures to drain an abscess or to treat an obstructive focus at any site, including urinary tract, biliary tract and surgical site, among others). Patients were classified as having sepsis or septic shock as described elsewhere in the Sepsis-3 consensus.[16] Moreover, the INCREMENT-CPE mortality score was calculated for every patient (regardless of whether or not they had documented bloodstream infection) using the model elaborated by Gutiérrez-Gutiérrez *et al.*[17]

A standard dosage was defined as 2.5 g (2000 mg ceftazidime and 500 mg avibactam) intravenously (iv) every 8 h, with adjustments for renal impairment made according to manufacturer recommendations.[18] Combination therapy was defined as the addition (iv or inhaled) of other antimicrobials with *in vitro* activity against the clinical isolate. Concomitant treatment with metronidazole (when, according to clinical criteria, coverage against anaerobes was required) was not considered as combination therapy. In each case, combination treatment, as well as the selection of a second agent, was started following consultation with the Infectious Diseases (ID) physician. In all cases susceptibility to the second antibiotic was confirmed before its initiation.

Clinical cure was defined as resolution of signs and symptoms of infection (assessed according to vital signs, the course of the SOFA score and laboratory data) within 7 days of treatment initiation. Microbiological failure was defined as isolation of CPE from a sample obtained from the same source of infection and/or blood cultures following $\geq$7 days of ceftazidime/avibactam treatment initiation. Microbiological cure was defined as sterilization of site-specific cultures and/or blood cultures after treatment ending and/or within 7 days after treatment initiation. Infection-related mortality was determined by one ID physician of the Infectious Diseases Unit. All cases were discussed in clinical session with the full team before treatment initiation. Recurrence within 90 days of onset was defined as microbiological failure and concomitant signs of infection.

Microbiological methods

All Enterobacteriaceae isolates in blood cultures or in other clinical samples were processed in the Laboratory of Microbiology of the Complejo Hospitalario Universitario de Vigo according to the current standardized procedures. Antibiotic susceptibility was determined by the VITEK2 (BioMérieux, France) automatic method. For the confirmation of ESBLs, a phenotypic method with a double Etest strip and/or a modified double disc was used.

The detection of carbapenemases was carried out following the EUCAST protocol: meropenem disc diameter $<$25 mm or MIC $>$0.12 mg/L in all Enterobacteriaceae. Confirmation was carried out with chromID medium CARBA SMART (BioMérieux) and the type of carbapenemase was determined by PCR (Cepheid Xpert Carba-R). There was no change in the method used for the identification of microorganisms or analysis of antibiotic susceptibility during the study period.

Susceptibility of bacteria to ceftazidime/avibactam was determined by the disc diffusion method as described elsewhere.[19] A disc diffusion zone diameter of $\geq$21 mm was interpreted as susceptible (equivalent to MIC $\leq$8/4 mg/L for ceftazidime/avibactam).

Statistical analysis

The statistical package SPSS v24.0 (SPSS, Chicago, IL, USA) was used for data analysis. Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test and were described as mean $\pm$ SD or as median (IQR) according to whether the distribution of the variables was normal or non-normal. The χ^2 test and Fisher's exact test were used to compare categorical variables.

Univariate analysis of factors potentially associated with 14 day mortality were analysed by Cox regression. Variables with a *P* value $<$0.20 in univariate analysis and those with potential clinical relevance were included in the Cox multivariate regression model and selected using a backwards process. Variables with a two-sided *P* value $<$0.05 were considered statistically

Table 1. Demographic and clinical characteristics of patients treated with ceftazidime/avibactam

Variable	Value
Total number of patients	57
Demographic characteristics	
age, years, median (range)	64 (26–86)
sex male, *n* (%)	44 (77)
Charlson index, median (IQR)	3 (0–13)
neoplasia, *n* (%)	14 (24)
chronic renal disease, *n* (%)	12 (21)
creatinine clearance <30 mL/min, *n* (%)	7 (12)
surgery in the previous month, *n* (%)	33 (58)
Location at onset of infection	
ICU/reanimation unit, *n* (%)	22 (38)
surgical department, *n* (%)	16 (28)
Antibiotic treatment before CAZ/AVI	51 (89)
carbapenems, *n* (%)	35 (61)
quinolones, *n* (%)	22 (38)
cephalosporins, *n* (%)	27 (47)
colistin, *n* (%)	29 (51)
Source of infection	
intra-abdominal, *n* (%)	16 (28)
pulmonary, *n* (%)	15 (26)
ventilator-associated, *n* (%)	7 (12)
urinary, *n* (%)	14 (25)
Bacteraemia, *n* (%)	26 (46)
abdominal source, *n* (%)	8 (14)
urinary source, *n* (%)	5 (9)
pulmonary source, *n* (%)	5 (9)
catheter-related, *n* (%)	6 (10)
other source, *n* (%)	6 (10)
Severity of infection	
sepsis/septic shock, *n* (%)	31 (54)
vasopressor use, *n* (%)	20 (35)
mechanical ventilation, *n* (%)	17 (30)
median APACHE-II (IQR)	24 (8–45)
INCREMENT-CPE score, median (IQR)	6 (2–13)

CAZ/AVI, ceftazidime/avibactam.

Table 2. Antimicrobial susceptibility of isolates ($n = 57$) from patients treated with ceftazidime/avibactam

Antibiotic	Susceptible isolates, *n* (%)
Colistin	43 (75)
Imipenem	2 (3)
Imipenem MIC <8 mg/L	27 (47)
Meropenem	1 (2)
Fosfomycin	10 (17)
Tigecycline	7 (12)
Amikacin	3 (5)
Ceftazidime/avibactam	57 (100)

significant. Moreover, a propensity score for receiving combination therapy was calculated using a multivariate logistic regression model in which the outcome variable was combination therapy. The following variables were introduced into the model: age, sex, Charlson index, inclusion criteria for receiving ceftazidime/avibactam, INCREMENT-CPE score, source of infection, source control, septic shock at onset and APACHE-II score.

Ethics

The study was approved by the local ethics committee (2017/336), which waived the need to obtain written informed consent and allowed us to use the information (previously collected) from our database. STROBE recommendations were followed.

Results

A total of 57 patients were included during the study period. Clinical and demographic characteristics of the patients are shown in Table 1. The median age was 64 years (range 26–86) and 77% (44/57) were male. All patients (38/57 prior to infection and the remaining patients after the diagnosis of infection due to CPE was made) had confirmation of intestinal colonization by CPE, performed through rectal swabs according to a local protocol endorsed by the Prevention and Infection Control Department. The median INCREMENT-CPE score was 6, and the score was >7 points in 40% (23/57) of cases. In 86% (49/57) of patients infection was hospital acquired. The most frequent source of infection was intra-abdominal (28% of cases, 16/57), followed by pulmonary (26%, 15/57, including 7 patients with ventilator-associated pneumonia) and urinary source (25%, 14/57). Bacteraemia was confirmed in 46% (26/57) of patients. Six patients received treatment with ceftazidime/avibactam for infrequent indications [severe skin and soft tissue infection (SSTI) ($n = 3$), ventriculitis with bacteraemia ($n = 1$), sternal osteomyelitis with bacteraemia ($n = 1$) and mediastinitis ($n = 1$)].

Most patients received ceftazidime/avibactam as monotherapy (81%, 46/57). Renal adjustment dose was required in 35% (20/57) of patients. Ceftazidime/avibactam was started because of previous treatment failure (all of them had received a combination of colistin plus imipenem in extended infusion) in 51% of cases (29/57), owing to absence of adequate treatment options in 42% (24/57) and toxicity of previous antibiotic treatment in the remaining 4 patients (7%). In most of them (53/57, 93%) ceftazidime/avibactam was initiated once *in vitro* susceptibility was confirmed, and was empirically started in four cases. The median time (IQR) from the onset of infection until the start of ceftazidime/avibactam was 5 days (0–13).

According to the microbiological profile, isolates were OXA-48-producing *K. pneumoniae* in 54 cases, *Escherichia coli* in 2 cases and *Enterobacter cloacae* in 1 case. Antimicrobial susceptibility of isolates is shown in Table 2. No isolate was susceptible to quinolones or cephalosporins.

Combination treatment was used in 11 patients (with iv colistin in 5, inhaled colistin in 2, tigecycline in 2 and amikacin and imipenem in 1 case each). Patients were treated with a second agent for a median of 13 days (IQR 5–15). Table 3 shows a comparison of demographic, clinical and treatment characteristics of patients receiving monotherapy versus combination treatment.

The median follow-up (IQR) of patients was 153 days (18–285). Clinical and microbiological cure were achieved in 77% and 65% of patients, respectively and microbiological failure was observed in 10% of cases. All-cause mortality rates assessed at 14 and 30 days

Table 3. Comparison of patients receiving monotherapy versus combination treatment with ceftazidime/avibactam

Variable	Monotherapy ($n = 46$)	Combination ($n = 11$)	*P* value
Age, years median (IQR)	69 (30–82)	58 (33–78)	0.21
Male sex, *n* (%)	35 (76)	9 (82)	0.68
Charlson index >2, *n* (%)	27 (59)	6 (55)	0.80
Hospital-acquired, *n* (%)	39 (85)	10 (91)	0.59
INCREMENT-CPE score >7, *n* (%)	19 (41)	4 (36)	0.76
Vasopressor use, *n* (%)	16 (35)	4 (36)	0.42
APACHE-II score, median (IQR)	20 (8–40)	23 (9–45)	0.13
CAZ/AVI started owing to previous treatment failure, *n* (%)	22 (48)	7 (64)	0.34
Source of infection, *n* (%)			
pulmonary	9 (20)	6 (54)	0.02
urinary	13 (28)	1 (9)	0.18
intra-abdominal	10 (22)	4 (36)	0.31
Source control procedure, *n* (%)	7 (15)	2 (18)	0.18
Time to start of treatment with CAZ/AVI, days, median (IQR)	2 (0–15)	4 (2–17)	0.11
14 day mortality, *n* (%)	7 (15)	1 (9)	0.42
30 day mortality, *n* (%)	10 (22)	3 (27)	0.69
90 day recurrence, *n* (%)	4 (9)	2 (18)	0.35
Clinical cure, *n* (%)	37 (80)	7 (64)	0.44
Microbiological cure, *n* (%)	31 (67)	6 (54)	0.58

CAZ/AVI, ceftazidime/avibactam.

were 14% and 22%, respectively. Infection-attributed 30 day mortality was 14% ($n = 8$), comprising three cases with pulmonary infection, two cases with urinary and intra-abdominal infection and one patient with a complicated SSTI. To identify predictors of treatment outcome, univariate and multivariate analyses by Cox regression of 14 day all-cause mortality risk factors were performed after adjusting by propensity score for receiving combination therapy, including the variables mentioned in the Statistical analysis section (Table 4). The only factor related to 14 day mortality was an INCREMENT-CPE score >7 (HR 11.7, 95% CI 4.2–20.6, $P = 0.001$).

In the subgroup of patients with intra-abdominal infection, which was the leading cause of infection ($n = 17$), an adequate source control was necessary (owing to the presence of deep-seated infections such as intra-abdominal or pelvic abscesses) in 53% (9/17) and it was achieved in all of them (including two patients who died: one case of severe necrotizing pancreatitis which was percutaneously drained and one case of colon perforation that required multiple surgical interventions). In this subgroup of patients, combination treatment (in addition to metronidazole) was used in only two patients and both patients died (on days 18 and 28 after diagnosis).

Recurrence of infection (evaluated at day 90) was observed in six patients (10%) with a median time of 41 days (IQR 9–71) from the end of treatment. These patients had been initially treated for a median of 13 days (IQR 10–16). All strains isolated at recurrence were confirmed to be OXA-48 producers, with no increase in ceftazidime/avibactam MIC compared with the original isolates. These patients were retreated with ceftazidime/avibactam monotherapy and all but one patient were clinically and microbiologically cured. The remaining patient, who had a complicated sternal osteomyelitis, achieved clinical and microbiological cure following a third course of ceftazidime/avibactam monotherapy. Furthermore, development of resistance to ceftazidime/avibactam was not detected in any patient during the whole follow-up period.

In regard to treatment safety, two patients developed acute kidney injury during ceftazidime/avibactam treatment (one of them on concomitant iv colistin) but discontinuation owing to side effects was required in no patient. In another two patients, a decrease in the level of consciousness ($n = 1$) and status epilepticus ($n = 1$) was observed a few days after the treatment had begun; however, this was related to the critical situation of the patient and the treatment was maintained with resolution of the neurological symptoms, which is why we believe that its association with ceftazidime/avibactam is unlikely. No other adverse effects related to ceftazidime/avibactam were observed.

Discussion

To our knowledge, this is one of the largest cohorts of patients with infections due to CPE treated with ceftazidime/avibactam. It is worth mentioning that in our study all patients were infected with OXA-48-type-producing Enterobacteriaceae, a type of microorganism very little represented in CPE clinical studies published until now.

In our cohort, the all-cause mortality rate (14% at 14 days and 22% at 30 days) was slightly lower than in previously reported studies with ceftazidime/avibactam in real clinical practice, which ranged from 24% to 39.5%.[11–13] Nevertheless, mortality in these studies was reported heterogeneously (30 day mortality, in-hospital mortality, or mortality related or not related to infection). In addition, the predominant carbapenemase type in previous studies was KPC (ranging from 57% to 78%).[11–13] Furthermore, although the demographic profile of patients was similar to that in our series, it should be noted that in Shields *et al.*[11] both infection severity (median APACHE-II score 34) and the number of transplant recipients (30%) were notably higher.

Table 4. Comparison of patients with and without all-cause 14 day mortality and multivariate Cox regression analysis of 14 day mortality risk factors with adjustment for propensity score for receiving combination therapy

	Univariate			Multivariate	
Variable	died ($n = 8$)	survived ($n = 49$)	*P* value	HR (95% CI)	*P* value
Age in years, median (IQR)	77 (50–82)	63 (28–79)	0.06		0.39
Male sex, *n* (%)	6 (75)	38 (77)	0.87	1.22 (0.5–2.8)	
Charlson index >2, *n* (%)	5 (62)	28 (57)	0.77	1.62 (0.4–2.3)	0.43
INCREMENT-CPE score >7, *n* (%)	8 (100)	15 (31)	0.001	11.70 (4.2–20.6)	**0.001**
Bacteraemia, *n* (%)	4 (50)	22 (45)	0.65	1.17 (0.3–5.6)	0.81
APACHE score >20, *n* (%)	3 (37)	14 (28)	0.39	1.93 (0.3–4.0)	0.64
Previous treatment failure, *n* (%)	5 (62)	24 (49)	0.48	1.82 (0.5–6.4)	0.34
Monotherapy, *n* (%)	7 (87)	39 (79)	0.42	1.72 (0.5–4.2)	0.55
Delay in CAZ/AVI start, days, median (IQR)	6 (1–13)	5 (1–11)	0.30	1.22 (0.2–3.3)	0.66
Source of infection, *n* (%)					
urinary	3 (37)	11 (22)	0.35	1.22 (0.2–3.1)	0.91
pulmonary	1 (12)	14 (28)	0.34	0.79 (0.2–2.5)	0.34
intra-abdominal	1 (12)	13 (26)	0.39	0.68 (0.4–3.1)	0.45

P values <0.05 are shown in bold.

In our cohort, using a Cox regression model, and adjusting for the propensity score for receiving combination treatment, an INCREMENT-CPE score >7 points was the only independent predictor of 14-day mortality. Although in Gutiérrez-Gutiérrez *et al.*[17] this score had been validated only in patients with bloodstream infections, our results shows that it can also be a good predictor of mortality in other types of CPE infection.

Recently, van Duin *et al.*[20] published a prospective cohort study of patients infected with carbapenemase-resistant Enterobacteriaceae (96% of them with KPC-producing *K. pneumoniae* infections) who received first-line treatment with ceftazidime/avibactam or colistin. In the group of patients treated with ceftazidime/avibactam, a very low 30 day mortality rate was observed (8%). Among the possible explanations for this finding, the cohort of van Duin *et al.* included younger patients (median age 57 versus 64 years), with fewer comorbidities (median Charlson index 2 versus 3) and a lower proportion of severe infections (18% versus 53%). In addition, ceftazidime/avibactam was started in most of our patients owing to failure of previous regimens or the absence of any other effective alternative.

In our series, the most frequent source of infection was intra-abdominal, followed by pneumonia and urinary tract infection. This contrasts with previous studies[11,12,20] in which a respiratory source was the most frequent (in the study of van Duin *et al.*[20] no cases of intra-abdominal infection were reported). The percentage of patients with bacteraemia in our series (45%) was consistent with previously reported data, ranging from 39%[20] to 68%.[12] It is worth noting that in our series six patients received treatment for infections for which ceftazidime/avibactam has not been evaluated (sternal osteomyelitis, mediastinitis and SSTI) with clinical cure in all of them, except one case with severe SSTI.

One of the most concerning issues observed in the study by Shields *et al.*[13] was the rate of recurrence (17%) and especially the appearance of ceftazidime/avibactam resistance in 10% (8/77) of patients who had been treated for a median of 15 days (range 7–31). In our series, the recurrence rate was lower (10%) and no cases of resistance were observed during or after treatment. In our six cases with infection recurrence, all were eventually cured following retreatment with ceftazidime/avibactam. Indeed, no resistant CPE strains have been isolated in our centre so far. This finding may be explained by the type of carbapenemase (OXA-48) prevalent in our institution. In agreement, resistance development during treatment was previously reported only in KPC-3[11,13,21] and KPC-2[22] strains.

The vast majority of patients in our series were treated with monotherapy (81%). In previous studies the percentages of combination treatment are disparate, ranging from 35% to 69%.[12,13,20] In the INCREMENT cohort, combination therapy using a carbapenem showed a benefit for the treatment of patients with high mortality risk. However, no patient was treated with ceftazidime/avibactam.[23]

In our study, monotherapy was not associated with higher 14 day mortality in multivariate analysis (with propensity score analysis including variables such as infection severity, source of infection and delay in targeted treatment initiation). However, the low number of patients receiving combination therapy ($n = 11$) prevents us from drawing further conclusions with regard to the benefit of combination therapy, mainly for patients at higher risk of mortality, with an INCREMENT-CPE score >7. Nevertheless, our experience with ceftazidime/avibactam monotherapy shows that clinical results are similar to those published with combination treatment.

Another notable feature in our study was the low number of observed adverse events during treatment. Two patients developed acute renal failure, but it was not necessary to interrupt treatment in either of them. In the paper by Temkin *et al.*[12] seizures and disorientation were also described, although their relationship with the use of ceftazidime/avibactam was not clear.

Our work has several limitations. The first is that most patients received ceftazidime/avibactam as rescue therapy, so our results

may not be generalizable to the entire population suitable for receiving treatment with it. On the other hand, as most of patients included in our series with severe infections are underrepresented in clinical trials, our results might offer greater evidence for the use of ceftazidime/avibactam in real clinical practice. An additional limitation includes the observational nature of this study. Although all the patients were prospectively evaluated by a member of our Infectious Diseases Unit, confounding by indication is a potential bias that we cannot exclude (many patients did not receive treatment with ceftazidime/avibactam because it was considered that they had a very poor prognosis in the short term or a very poor baseline quality of life). Moreover, our cohort includes only OXA-48-type isolates, so the results may not be extrapolated to another type of CPE.

In summary, our study included the largest cohort of patients with invasive OXA-48 CPE infections treated with ceftazidime/avibactam. Our study shows promising results for patients with limited therapeutic options. Although the sample size is limited, we have not observed the appearance of resistance during or after treatment with ceftazidime/avibactam.

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Transparency declarations

None to declare.

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