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Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

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Background. In vitro data support the use of combination of aztreonam (ATM) with ceftazidime-avibactam (CAZ-AVI), but clinical studies are lacking. The aim of our study was to compare the outcome of patients with bloodstream infections (BSIs) due to metallo-β-lactamase (MBL)–producing Enterobacterales treated either with CAZ-AVI plus ATM or other active antibiotics (OAAs).

Methods. This was a prospective observational study including patients admitted to 3 hospitals in Italy and Greece. The primary outcome measure was 30-day all-cause mortality. Secondary outcomes were clinical failure at day 14 and length of stay after BSI diagnosis. Cox regression analysis including a propensity score (PS) for receiving CAZ-AVI + ATM was performed to evaluate primary and secondary outcomes. A PS-based matched analysis was also performed.

Results. We enrolled 102 patients with BSI; 82 had infections caused by NDM-producing (79 *Klebsiella pneumoniae* and 3 *Escherichia coli*) and 20 by VIM-producing (14 *K. pneumoniae*, 5 *Enterobacter* species, 1 *Morganella morganii*) strains. The 30-day mortality rate was 19.2% in the CAZ-AVI + ATM group vs 44% in the OAA group ($P = .007$). The PS-adjusted analysis showed that the use of CAZ-AVI + ATM was associated with lower 30-day mortality (hazard ratio [HR], 0.37 [95% confidence interval {CI}, .13–.74]; $P = .01$), lower clinical failure at day 14 (HR, 0.30 [95% CI, .14–.65]; $P = .002$), and shorter length of stay (subdistributional HR, 0.49 [95% CI, .30–.82]; $P = .007$). The PS-matched analysis confirmed these findings.

Conclusions. The CAZ-AVI + ATM combination offers a therapeutic advantage compared to OAAs for patients with BSI due to MBL-producing Enterobacterales. Further studies are warranted.

Keywords. metallo-β lactamases; NDM; ceftazidime-avibactam; aztreonam; bloodstream infections.

Metallo-β-lactamase (MBL)–producing Enterobacterales are endemic in the Indian subcontinent [1] but are increasingly reported as cause of healthcare-associated infections in Europe and worldwide [2–6]. Bloodstream infections (BSIs) due to carbapenem-resistant MBL-producing isolates are associated with mortality rates > 30% [1, 5].

MBLs (New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], and Imipenem hydrolyzing beta-lactamase [IMP]) are able to inactivate all β-lactams except aztreonam (ATM). However, ATM cannot be used alone because of the concomitant co-production of other enzymes (extended-spectrum β-lactamases, *Klebsiella pneumoniae* carbapenemase [KPC], and other cephalosporinases) by MBL-producing bacteria [7, 8]. The optimal regimen for treating patients with BSIs due to MBL-producing organisms is not well defined, and clinical experience with the use of the few in vitro–active antibiotics (colistin, fosfomycin, tigecycline) is limited [9–12]. The combination of ceftazidime-avibactam (CAZ-AVI) plus ATM is also considered as a potential therapeutic option [13, 14], but only case reports or small case series [15–20] have been published.

We therefore evaluated the impact of the combination CAZ-AVI + ATM compared to other targeted active antibiotic regimens on the outcome of patients with BSI due to MBL-producing Enterobacterales.

METHODS

This was an observational prospective study performed in 2 Italian hospitals (Pisa and Livorno) and 1 Greek hospital (Laiko General Hospital, Athens), between November 2018 and December 2019. Patients were eligible for inclusion in the study if they were (1) ≥ 18 years old, (2) had a blood culture positive for MBL-producing Enterobacterales, and (3) received therapy with ≥ 1 antimicrobial showing in vitro activity against the

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MBL-producing isolate for at least 48 hours. All patients were followed up until 30 days after the BSI episode. The study was conducted according to the principles stated in the Declaration of Helsinki. The ethics committees of the participating hospitals approved the study protocol.

Bacterial Isolates Identification and Susceptibility Testing

Blood isolate identification was performed by matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI Biotyper, Bruker Daltonics) or Wider I (Dade Behring MicroScan). The presence of the *bla* genes for MBLs (NDM, VIM, IMP) was determined by polymerase chain reaction using the GeneXpert System (Cepheid) directly from positive blood culture bottles [21]. Antimicrobial susceptibility tests were performed with the SensiTitre system (Thermo Fisher Scientific), according to the manufacturer's instructions. Minimum inhibitory concentrations (MICs) were classified according to breakpoints established by the European Committee on Antimicrobial Susceptibility Testing [22].

Synergy between CAZ-AVI and ATM was screened by double-disk synergy test and evaluated by gradient-test superposition method [23]; the combination of 2 antibiotics was considered synergistic if an inhibition zone between the 2 disks became evident and if CAZ-AVI reduced ATM MIC below its susceptibility cutoff. Supplementary Figure 1 shows the synergistic activity of CAZ-AVI and ATM in 1 clinical isolate.

Antibiotic Therapy

Patients were treated with targeted antibiotic regimens chosen by an infectious disease (ID) specialist on the basis of the phenotypic profile of the blood isolate. The pool of ID prescribers was composed by 5 independent physicians. At the time of antibiotic selection, ID consultants were blinded to the study results.

CAZ-AVI was administered at the dose of 2.5 g every 8 hours and ATM at the dose of 2 g every 8 hours. Colistin was administered with a loading dose of 9M IU followed by 4.5M IU every 12 hours; tigecycline as 100 mg twice daily; fosfomycin 4–6 mg every 6 hours; gentamicin 3–5 mg/kg as a single daily dose; and meropenem 2 g every 8 hours. Loading doses were used for colistin and tigecycline. All doses were adjusted for creatinine clearance.

Study Outcome Variables

The main outcome variable was the 30-day all-cause mortality, defined as the occurrence of death within 30 days from the index blood culture.

Secondary outcomes were clinical failure at day 14 and length of hospital stay (LOS) after the BSI episode. Clinical failure was defined as death or a lack of clinical or microbiological improvement [24]. The main exposure of interest was targeted antibiotic therapy with either CAZ-AVI + ATM or other active antibiotics (OAAs). "OAAs" was defined as an antibiotic regimen including at least 1 in vitro–active drug [24]. Treatment was classified as monotherapy or combination therapy according to the number of in vitro–active drugs administered.

Predictors of Mortality

Patient variables explored as predictors of mortality included age, sex, Charlson comorbidity index, underlying diseases, immunosuppressive therapy, history of previous hospitalization, previous surgery (30 days), radiotherapy or chemotherapy (in the previous 3 months), and previous antimicrobial therapy [25].

Other variables considered were septic shock, Sequential Organ Failure Assessment (SOFA) score, mechanical ventilation, source of infection (defined according to Centers for Disease Control and Prevention definitions [26]), control of removable source of infection, and acute kidney injury (AKI). Control of removable source of infection was defined as removal of any preexisting contaminated intravascular device and drainage of intra-abdominal abscesses or other fluid collections thought to be the source of infection [27]. AKI was defined as an abrupt (within 48 hours) increase in serum creatinine of 0.5 mg/dL or a 50% increase above baseline for at least 2 repeated measurements [28].

Statistical Analysis

Continuous variables were reported as mean ± standard deviation or median and interquartile range according to their distribution. The normality of distributions was assessed by the Kolmogorov-Smirnov test. Continuous variables were compared by the Student *t* test or the Mann-Whitney *U* test, as appropriate. Categorical data were expressed as frequency distributions, and the χ^2 test or Fisher exact test was used to determine if differences existed between groups.

According to the study outcome, univariate and multivariate analyses were performed using Cox proportional hazards regression to identify associations between exposures and mortality until day 30 or clinical failure at day 14, respectively. All variables were considered for the multivariate model. Targeted antibiotic therapy was used as covariate, and CAZ-AVI + ATM was tested against OAAs. The final multivariate model was chosen according to the Akaike information criterion, and to parsimony and clinical interpretability of data.

Propensity scores (PS) were estimated to explore the causal effect of treatment under selection-on-observables assumption. The PS was estimated through logistic regression as the logistic transform of the probability of receiving CAZ-AVI + ATM. The final PS model had an area under the receiver operating characteristic curve ≥ 0.80. We determined the candidate variables referring to all potential risk factors for death reported in previous studies. The variables included age, intensive care

unit (ICU) hospitalization, solid cancer, diabetes mellitus, solid organ transplantation, chronic obstructive pulmonary disease, cardiovascular disease, chronic kidney failure, septic shock, and urinary tract as source of infection. Considering the potential bias due to prescription by different ID consultants, we also included in the PS the variable "ID prescriber." The PS was used as a covariate in multivariate analysis, and also for matching. In the first case, hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for a model including treatment and PS. With regards to LOS from BSI onset, the competing risk of death was considered, and therefore subdistributional HRs (sHRs) were calculated on the basis of the Fine and Gray model. For the case of matching, patients treated with CAZ-AVI + ATM and those who received OAAs were matched 1:1 using a greedy matching procedure without replacement. The Cox and the Fine and Gray regression analyses were then repeated on the matched patients as confirmatory analysis.

Cumulative incidence was estimated using the Kaplan-Meier product-limit estimator; nonparametric (log-rank) tests were used to compare survival functions in different groups. Sensitivity analysis were performed to evaluate the effect of combination therapy (defined as reported above) and the start of active antibiotic therapy within the first 48 hours from BSI onset on 30-day mortality.

Statistical significance was established at $P \leq .05$. All reported P values are 2-tailed. The results obtained were analyzed using commercially available statistical software packages (IBM SPSS version 22.0, Armonk, New York; and R version 3.5.1, Vienna, Austria).

Table 1. In Vitro Susceptibilities of 102 Metallo-β-Lactamase–Producing Blood Isolates

	MIC, mg/L	Susceptibility Rate, %	
Bacterial Species and Antimicrobial Agent Tested	Range	Susceptible	Resistant
NDM-producing (n = 82)			
Ceftriaxone	>4	…	100
Ceftazidime	>64	…	100
Cefepime	>16	…	100
Piperacillin-tazobactam	>128/4	…	100
Ciprofloxacin	>1	…	100
Levofloxacin	>8	…	100
Amikacin	<2 to >32	6.1	93.9
Gentamicin	<1 to >16	8.5	91.5
Meropenem	≤0.125 to 64	6.1	93.9
Ertapenem	1 to >2	…	100
TMP-SMX	≤2/38 to >8/152	2.4	97.6
Tigecycline	≤0.25 to >4	84.1	15.9
Colistin	≤0.5 to >8	90.2	9.8
Fosfomycin	4 to 64	72	28
Aztreonam	<2 to >32	7.3	92.7
CAZ-AVI	>32	…	100
VIM-producing (n = 20)			
Ceftriaxone	>4	…	100
Ceftazidime	>64	…	100
Cefepime	>16	…	100
Piperacillin-tazobactam	>128/4	…	100
Ciprofloxacin	>1	…	100
Levofloxacin	>8	…	100
Amikacin	<2 to >32	5	95
Gentamicin	<2 to >16	20	80
Meropenem	2 to >64	25	75
Ertapenem	1 to >2	…	100
TMP-SMX	>4/76	…	100
Tigecycline	<0.5 to 6	50	50
Colistin	≤0.5 to >8	80	20
Fosfomycin	4 to 64	80	20
Aztreonam	<2 to >32	50	50
CAZ-AVI	>32	…	100

Abbreviations: CAZ-AVI, ceftazidime-avibactam; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; TMP-SMX, trimethoprim-sulfamethoxazole; VIM, Verona integron-encoded metallo-β-lactamase.

Table 2. Targeted Antibiotic Regimens Administered in 102 Bloodstream Infections Due to Metallo-β-Lactamase–Producing Enterobacterales

Antibiotic Regimen	No. (%) (N = 102)	Mortality, No. (%)
CAZ-AVI + ATM[a]	52 (51)	10/52 (19.2)
OAAs		
Colistin-containing regimens	27 (26.5)	16/27 (59.3)
Colistin + fosfomycin + tigecycline	7	6/7
Colistin + fosfomycin	7	5/7
Colistin + meropenem	5	3/5
Colistin + ATM ± piperacillin-tazobactam	4	1/4
Colistin + gentamicin	1	0/1
Colistin + cotrimoxazole	1	0/1
Colistin alone	2	1/2
Regimens not containing colistin	23 (22.5)	6/23 (26.1)
Tigecycline + aminoglycosides	8	2/8
Fosfomycin + aminoglycosides	5	0/5
Tigecycline + fosfomycin	2	2/2
Tigecycline + meropenem	1	0/1
ATM + aminoglycosides	4	1/4
ATM + fosfomycin	1	0/1
ATM alone	2	1/2

Abbreviations: ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; OAAs, other active antibiotics.
[a]In vitro activity is supported by in vitro synergistic tests.

RESULTS

Overall, 107 episodes of BSIs caused by MBL-producing Enterobacterales were documented in the study period. Five patients died before initiation of in vitro–active antibiotic therapy and were excluded from the analysis. One hundred two patients with MBL-producing Enterobacterales were finally included in the study: of these, 82 were caused by NDM-producing strains (79 *K. pneumoniae*, 3 *Escherichia coli*) and 20 by VIM-producing strains (14 *K. pneumoniae*, 5 *Enterobacter* species, 1 *Morganella morganii*).

Table 1 shows in vitro susceptibility patterns of all included isolates. Antibiotics active against the majority of NDM- and VIM-producing strains were, respectively: colistin (90.2% and 80%), tigecycline (84.1% and 50%), and fosfomycin (72% and 80%). ATM alone was active against 50% of VIM strains and 7.3% of NDM isolates. Synergy between CAZ-AVI and ATM was documented in all cases treated with this combination (47 NDM- and 5 VIM-producing strains).

Overall, 52 (51%) patients received a combination therapy of CAZ-AVI + ATM, whereas 50 (49%) were treated with OAAs. In the CAZ-AVI + ATM group, CAZ-AVI was administered as a prolonged 8-hour infusion in 26 patients (50%), and in the remaining cases was administered in a 2-hour infusion 3 times daily. ATM was administered as a 2-hour bolus infusion. Three patients of the CAZ-AVI + ATM group were initially treated (for < 48 hours) with other antibiotics: 2 patients switched from tigecycline plus fosfomycin or colistin to CAZ-AVI + ATM due to nausea and vomiting, and 1 from fosfomycin plus amikacin because of the worsening of clinical conditions. Among patients of the OAA group, 23 (46%) received ≥ 2 in vitro–active agents, while the remaining patients received a single active agent. Meropenem was administered in prolonged 6- to 8-hour infusion in all cases. A description of the antibiotic regimens with the related mortality rates is shown in Table 2. Clinical features and outcomes of the 2 treatment groups are summarized in Table 3. The groups were similar, with the exception of ICU care, which was more frequent in the CAZ-AVI + ATM group ($P = .001$), whereas surgical ward acquisition and immunosuppressive therapy were more common in the OAA group ($P = .03$ and $P = .001$, respectively).

Primary Outcome Analysis

The 30-day mortality rate was significantly lower for the CAZ-AVI + ATM group than the OAA group (19.2% vs 44%, respectively; $P = .007$). Among patients treated with colistin-based regimens, the mortality was 59.3% (16 deaths), compared with 26.1% (6 deaths) in those receiving regimens not containing colistin ($P = .019$). A total of 11 patients (10.8%) experienced drug-induced AKI (10 patients [20%] in the OAA group and 1 patient [1.9%] in the CAZ-AVI + ATM group; $P = .003$); 9 of 10 patients of the OAA group developing AKI received a colistin-containing regimen.

The multivariate Cox regression model showed that cardiovascular disease (HR, 6.62 [95% CI, 2.77–15.78]; $P < .001$), solid organ transplantation (HR, 3.52 [95% CI, 1.42–8.69]; $P = .006$), and SOFA score (HR, 1.21 [95% CI, 1.1–1.32]; $P < .001$) were factors independently associated with 30-day mortality, whereas treatment with CAZ-AVI + ATM was protective (HR, 0.17 [95% CI, .07–.41]; $P < .001$) (Table 4). The PS-adjusted analysis confirmed that CAZ-AVI + ATM was associated with lower risk of 30-day mortality (HR, 0.37 [95% CI, .13–.74]; $P = .01$). The unadjusted and PS-adjusted analyses performed after the exclusion of the 3 switch-over cases confirmed the same results (data not shown). The Kaplan-Meier survival curves of the 2 treatment groups are illustrated in Figure 1.

Secondary Outcomes Analysis

The analysis of the factors associated with clinical failure at day 14 shows that CAZ-AVI + ATM was associated with reduced risk (adjusted HR, 0.2 [95% CI, .08–.48]; $P < .001$) (Supplementary Table 1).

PS-adjusted analysis for secondary endpoints shows that CAZ-AVI + ATM was associated with lower risk of clinical failure at day 14 (HR, 0.30 [95% CI, .14–.65]; $P = .002$). Considering the competing risk of death, LOS from BSI onset was shorter in patients treated with CAZ-AVI + ATM (sHR,

Table 3. Clinical Characteristics and Outcomes of Patients With Bloodstream Infection Due to Metallo-β-Lactamase–Producing Enterobacterales, by Treatment Regimen

Characteristic	Overall (N = 102)	CAZ-AVI + ATM (n = 52)	OAAs (n = 50)	*P* Value
Age, y, median (IQR)	70 (55–78)	69 (49.75–77)	70.5 (57.5–78)	.247
Male sex	69 (67.6)	36 (69.2)	33 (66)	.727
Ward of hospitalization				
Medical ward	49 (48)	21 (40.4)	28 (56)	.115
ICU ward	35 (34.3)	26 (50)	9 (18)	**.001**
Surgery	18 (17.6)	5 (9.6)	13 (26)	**.030**
Comorbidities				
Cardiovascular disease	41 (40.2)	22 (42.3)	19 (38)	.657
Solid cancer	35 (34.3)	16 (30.8)	19 (38)	.442
COPD	20 (19.6)	6 (11.5)	14 (28)	**.036**
Diabetes	34 (33.3)	20 (38.5)	14 (28)	.263
Chronic renal disease	15 (14.7)	8 (15.4)	7 (14)	.844
Chronic liver failure	10 (9.8)	3 (5.8)	7 (14)	.162
Solid organ transplantation	8 (7.8)	2 (3.8)	6 (12)	.126
Charlson comorbidity index, median (IQR)	4 (2–6.25)	4 (1–6)	4.5 (2–7)	.339
Immunosuppressive therapy, previous 30 d	35 (34.3)	10 (19.2)	25 (50)	**.001**
Source of infection				
Unknown	14 (13.7)	5 (9.6)	9 (18)	.219
Urinary tract	33 (32.4)	13 (25)	20 (40)	.105
Intravascular device	27 (26.5)	17 (32.7)	10 (20)	.146
Skin and soft tissue	12 (11.8)	9 (17.3)	3 (6)	.076
Respiratory tract	9 (8.8)	6 (11.5)	3 (6)	.324
Intra-abdominal	7 (6.9)	2 (3.8)	5 (10)	.219
Source control	58 (56.9)	34 (65.4)	24 (48)	.076
SOFA score, median (IQR)	4 (2–7)	4 (2–6)	5 (2–7.5)	.383
Septic shock	27 (26.5)	13 (25)	14 (28)	.731
Mechanical ventilation	31 (30.4)	17 (32.7)	14 (28)	.607
Time to in vitro active therapy ≤ 48 h	71 (69.6)	40 (76.9)	31 (62)	.101
Drug-induced AKI	11 (10.8)	1 (1.9)	10 (20)	**.003**
Duration of antibiotic therapy, d, median (IQR)	10 (7–14)	11 (8–14)	9 (5.75–12.5)	.081
Primary outcome				
30-d mortality	32 (31.4)	10 (19.2)	22 (44)	**.007**
Secondary outcome measures				
Clinical failure at day 14	39 (38.2)	13 (25)	26 (52)	**.005**
LOS after BSI[a], median (IQR)	16.5 (10–31.5)	14 (10–20.25)	23 (9.5–42.75)	.135

Data are presented as no. (%) unless otherwise indicated. *P* values in bold are statistically significant.

Abbreviations: AKI, acute kidney injury; ATM, aztreonam; BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; OAAs, other active antibiotics; SOFA, Sequential Organ Failure Assessment.

[a]Calculated in patients discharged alive.

0.49 [95% CI, .30–.82]; *P* = .007) compared with those who received OAAs (Table 5).

Propensity Score–Matched Analysis for Primary and Secondary Endpoints

We performed a PS-based matched analysis for both primary and secondary endpoints; 50 pairs of patients treated with CAZ-AVI + ATM and OAAs were matched according to PS. Conditional logistic regression in PS-matched cohorts showed that CAZ-AVI + ATM was associated with a lower 30-day mortality rate (HR, 0.31 [95% CI, .15–.66]; *P* = .002), lower risk of clinical failure at day 14 (odds ratio, 0.36 [95% CI, .18–.7]; *P* = .003) and shorter length of hospital stay (sHR, 0.48 [95% CI, .29–.78]; *P* = .003) compared to patients who received other treatment regimens.

DISCUSSION

The main finding of our study is that the combination CAZ-AVI + ATM has a favorable impact on the outcome of patients with BSI caused by MBL-producing Enterobacterales. Compared to OAAs, we demonstrated a therapeutic advantage of the CAZ-AVI + ATM combination even after adjustment for baseline conditions and PS matching, with a reduction in the risk of mortality of about 60%. We also found that patients treated with this regimen are at lowest risk of clinical failure at day 14 from BSI onset and have shorter LOS.

Our results corroborate previous microbiological studies indicating the synergistic in vitro activity of the combination CAZ-AVI + ATM against MBL-producing Enterobacterales

Table 4. Cox Regression Analysis of Factors Independently Associated With 30-Day Mortality

Factor	HR (95% CI)	*P* Value
Cardiovascular disease	6.62 (2.77–15.78)	<.001
Solid organ transplantation	3.52 (1.42–8.69)	.006
SOFA score (1-point increment)	1.21 (1.1–1.32)	<.001
CAZ-AVI + ATM (vs OAAs)	0.17 (.07–.41)	<.001

Abbreviations: ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; HR, hazard ratio; OAAs, other active antibiotics; SOFA, Sequential Organ Failure Assessment.

[7]. Data on clinical efficacy and safety of this combination are limited to a few case reports [15–20], and our cohort is the largest published to date. As such, our study can provide valuable insights into the clinical role of this new antibiotic combination. Among patients who received OAAs, the highest 30-day mortality was observed in those treated with colistin-based regimens (59.3%). Therefore, the treatment with colistin appears to be associated with worse outcome. Moreover, drug-induced AKI was observed in 33.3% of patients receiving colistin, compared to 1.9% of those treated with CAZ-AVI + ATM and 4.3% of those with antimicrobial agents other than colistin. These data are not surprising; we recently demonstrated that in patients with BSI due to KPC-producing *K. pneumoniae*, CAZ-AVI was associated with a reduced risk of a composite endpoint of mortality or nephrotoxicity compared to colistin-containing regimens [27]. The risk of colistin-induced nephrotoxicity is well documented by previous clinical studies, ranging from 15% [29] to > 50% [30].

The optimum pharmacokinetic/pharmacodynamic (PK/PD) target for AVI in combination with CAZ and ATM is not yet determined. A joint attainment of 50% of unbounded fraction of the drug (fT) > 8 mg/L for ceftazidime and 50% fT > 1 mg/L for avibactam is considered as the main PK/PD target for CAZ-AVI, and the probability of target attainment is > 90% with the recommended dosing regimen [31]. Similarly, 1500/500 mg of ATM/AVI every 6 hours is predicted to achieve joint PK/PD target attainment in > 90% of patients [32]. In a recent study, Yasmin et al, using CAZ-AVI as a 50 mg/kg prolonged 3-hour infusion every 8 hours and ATM 50 mg/kg every 8 hours in a 4-year old boy, achieved sufficient free serum concentrations of AVI in synchrony with that of CAZ and ATM [16]. In the present study, the standard dosages of CAZ-AVI and ATM appeared to be adequate to obtain favorable clinical response. Further studies, however, are needed to assess the required PK/PD target and determine the optimal dosing regimen of CAZ-AVI and ATM when used in combination.

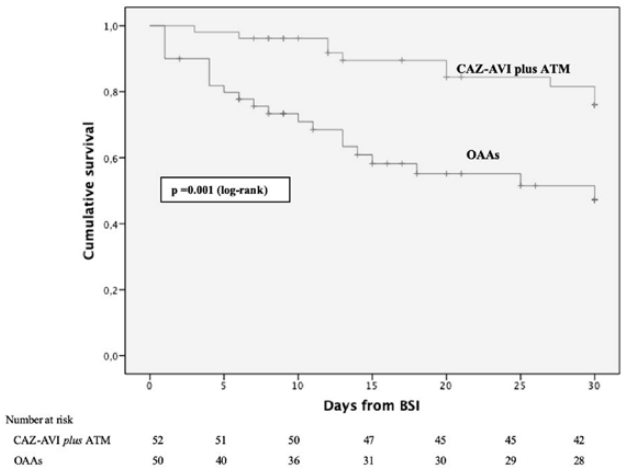

Figure 1. Kaplan-Meier survival curves according to treatment regimen (ceftazidime-avibactam plus aztreonam vs other active antibiotics). Abbreviations: ATM, aztreonam; BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; OAA, other active antibiotics.

A recent study showed that current antimicrobial susceptibility testing (AST) methods for defining the MICs of MBLs-producing strains may be inadequate for determining the MIC to meropenem, because of the impact of zinc concentrations in the AST media [33]. In our study, among 6 patients who received meropenem (5 in combination with colistin and 1 with tigecycline), 3 died (all in the group of colistin-containing regimens). Further clinical studies are needed to well define the potential use of carbapenems in combination with other antibiotics in patients with BSI due to MBL-producing isolates.

Our findings should not be interpreted without considering several limitations. First, it was a nonrandomized observational study with the inherent shortcomings of these studies. However, it should be mentioned that (1) we included all consecutive patients with BSIs caused by MBL-producing Enterobacterales diagnosed in the participating hospitals, thus avoiding selection bias; (2) the 2 treatment groups (CAZ-AVI + ATM vs OAAs) were well balanced regarding the variables with potential impact on outcome; and (3) a PS-based matched analysis was performed to control for potential bias on treatment selection. Second, the sample size was not large enough; the differences, however, between the 2 treatment groups achieved statistical significance that persisted after multivariate Cox regression analysis and even after PS adjustment. Third, as this is an observational, nonrandomized study, the prescriber may have influenced the treatment assignment and introduced a prescription bias. To overcome this bias, we included the variable "ID prescriber" in the PS. Moreover, ID prescribers were blinded to results at the time of prescription, and there were no differences in severity of illness between the 2 treatment groups. Finally, no therapeutic drug monitoring was performed to correlate the PK/PD profiles of CAZ-AVI and ATM with clinical outcomes.

Notwithstanding these limitations, the data presented herein provide practical and useful information that may assist clinicians to adopt more effective approaches for treatment of infections caused by MBL-producing Enterobacterales. The combination CAZ-AVI + ATM may be a suitable therapeutic

Table 5. Propensity Score–Adjusted Analysis for Secondary Study Endpoints

CAZ-AVI + ATM	HR (95% CI)	sHR[a] (95% CI)	*P* Value
Clinical failure at day 14	0.30 (.14–.65)	…	.002
Length of hospital stay from BSI onset[a]	…	0.49 (.30–.82)	.007

Abbreviations: ATM, aztreonam; BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam, CI, confidence interval; HR, hazard ratio; sHR, subdistributional hazard ratio.

[a]The sHR expresses the risk for 1-day increase.

option to treat patients with BSIs caused by MBL-producing Enterobacterales. This regimen was associated with clear survival benefits relative to other currently available therapeutic options, as well as with lower rate of clinical failure at day 14 and with shorter LOS after the BSI onset. Further studies are needed to identify the optimal regimen for the treatment of carbapenem-resistant MBL-producing Enterobacterales infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. F., F. M., and G. L. D. conceived of and designed the study. D. B., V. G., E. T., S. S., and L. G. recruited patients and collected clinical data. G. T. developed the database and analyzed and interpreted data. A. F. performed the propensity score analysis. C. G., A. L., and S. B. performed microbiological analysis. G. T., M. F., and F. M. wrote the manuscript. All authors contributed to the critical revision of the final manuscript.

Potential conflicts of interest. F. M. has participated in advisory boards and/or received speaker honoraria from Angelini, Correvio, Merck Sharp & Dohme (MSD), Nordic Pharma, Pfizer, Astellas, Gilead, Bristol-Myers Squibb (BMS), Janssen, ViiV, bioMérieux, Biotest, Becton Dickinson, Pfizer, and Shionogi. M. F. has received grants and speaker honoraria from MSD, Angelini, Shionogi, and Nordic Pharma. G. L. D. is a member of the speaker's bureaus for Pfizer, Rempex, and Menarini and has received grants from the European Commission FP7 AIDA Project. All declared conflicts of interest are outside the submitted work. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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