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Could an optimized joint pharmacokinetic/pharmacodynamic target attainment of continuous infusion ceftazidime-avibactam be a way to avoid the need for combo therapy in the targeted treatment of deep-seated DTR Gram-negative infections?

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ABSTRACT The objective of this study was to assess the relationship between joint pharmacokinetic/pharmacodynamic (PK/PD) target attainment of continuous infusion (CI) ceftazidime-avibactam and the microbiological outcome of documented difficult-to-treat resistant (DTR) Gram-negative infections. A 2-year retrospective cohort study was performed in patients receiving CI ceftazidime-avibactam mono- or combo therapy for documented DTR Gram-negative infections and undergoing therapeutic drug monitoring of both ceftazidime and avibactam. The free fractions of steady-state concentrations (fC_{ss}) of ceftazidime and avibactam were calculated. The joint PK/PD target was considered optimal when both the fC_{ss}/MIC ratio for ceftazidime ≥4 (equivalent to 100% $fT_{>4xMIC}$) and the fC_{ss}/C_T ratio for avibactam >1 (equivalent to 100% $fT >C_T$ of 4.0 mg/L) were simultaneously achieved (quasi-optimal if only one of the two and suboptimal if neither of the two was achieved). Multivariate logistic regression analysis was applied for testing potential variables associated with microbiological failure. Fifty-eight patients were treated with CI ceftazidime-avibactam mono- (36) or combo therapy (22) for documented DTR Gram-negative infections [74.2% for primary or secondary bloodstream infections (BSIs)]. Combo therapy was administered more frequently to intensive care unit (ICU) patients (P = 0.023) or for pneumonia (P = 0.001) and less frequently for intra-abdominal infections and BSIs (P = 0.04). Microbiological failure occurred in five cases (8.6%, three in mono- and two in combo therapy). In the multivariate analysis, the suboptimal/quasi-optimal joint PK/PD target emerged as the only independent predictor of microbiological failure (odds ratio [OR] 11.11; 95% confidence interval [CI] 1.31–93.98; P = 0.023), whereas monotherapy was not (P = 0.99). Optimized joint PK/PD target attainment of CI ceftazidime-avibactam monotherapy could represent a way forward for allowing microbiological eradication of DTR Gram-negative infections and could render unnecessary combo therapy.

KEYWORDS ceftazidime-avibactam, therapeutic drug monitoring, continuous infusion, joint PK/PD target, microbiological eradication, combination therapy

Difficult-to-treat resistant (DTR) Gram-negatives may represent major causes of severe hospital-acquired infections and mortality (1). Ceftazidime-avibactam is a novel beta-lactam/beta-lactamase inhibitor combination (BL/BLIc), which is widely used for targeted therapy of DTR Gram-negative infections caused by carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp), OXA-48-producing *Enterobacterales*, and DTR *Pseudomonas aeruginosa* (DTR-PA) (2).

Some early clinical studies suggested that the efficacy of ceftazidime-avibactam may be affected by the site of infection. Shields and co-workers showed that among

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77 patients receiving ceftazidime-avibactam for the treatment of carbapenem-resistant *Enterobacterales* (CRE) infections, the clinical success rates were lowest for pneumonia (36%) and higher for bacteremia (75%) and urinary tract infections (88%) (3). Additionally, in the multivariate analysis, pneumonia (P = 0.045) was associated with clinical failure. These findings were possibly attributed to suboptimal exposure at the infection site, so alternative ceftazidime-avibactam dosing and therapeutic regimens were advocated for improving the poor outcome in this setting. Consequently, several clinicians started using ceftazidime-avibactam in combination therapy for treating deep-seated DTR Gram-negative infections. In this regard, Tumbarello et al. recently showed that among a retrospective cohort of 577 adults treated with ceftazidime-avibactam for KPC-Kp infections, there was no significant difference in the mortality rate between patients receiving monotherapy and those receiving combination regimens (26.1% vs 25.0%; P = 0.79) (4). In the multivariate analysis, lower respiratory tract infections were still associated with increased mortality (P = 0.04), but interestingly, administration by prolonged infusion resulted in reduced mortality (P = 0.006) (4).

In this latter regard, continuous infusion (CI) may represent the best administration modality for achieving aggressive pharmacokinetic/pharmacodynamic (PK/PD) targets with beta-lactams under the same daily dose (5). It has been shown that PK/PD targets up to 100% $T_{>4\text{-}8xMIC}$ may be helpful for maximizing clinical efficacy and microbiological eradication and for minimizing the risk of resistance development with beta-lactams (6, 7). In regard to avibactam, it was recently shown that increasing avibactam concentrations may result in increased clinical efficacy and in a lower propensity of developing resistance among patients treated with ceftazidime-avibactam (8–10). This argues in favor of the fact that PK/PD targets for both ceftazidime and avibactam should be taken into account when assessing the efficacy of this BL/BLIc. We recently introduced the concept of a joint PK/PD target for ceftazidime-avibactam (10) and found that optimal joint PK/PD target attainment of CI ceftazidime-avibactam led to microbiological eradication of most of the DTR Gram-negative infections affecting two descriptive series of critically ill patients (10, 11).

The aim of this study was to test by multivariate logistic regression analysis whether the joint PK/PD target of ceftazidime-avibactam could represent a variable associated with the microbiological outcome in a retrospective cohort of patients affected by documented DTR Gram-negative infections treated with CI ceftazidime-avibactam mono- or combo therapy.

RESULTS

Overall, a total of 87 patients treated with ceftazidime-avibactam were retrieved during the study period, of whom 58 met the inclusion criteria (Fig. 1). Demographics and clinical features are shown in Table 1. The median [interquartile range (IQR)] age was 62.5 (55.5–73.8) years with male preponderance (62.1%). Intensive care unit (ICU) admission was needed in just over half of the patients (53.4%). Six out of 58 patients (10.3%) had augmented renal clearance (ARC), 15 underwent continuous renal replacement therapy (CRRT) (25.9%), and 1 underwent intermittent hemodialysis (1.7%). The most frequent underlying disease was hepatic cirrhosis (15.5%), followed by severe COVID-19 infection, febrile neutropenia, and solid organ transplantation (13.8% each). Sixteen out of 58 patients were immunosuppressed (27.6%). The most frequent types of infection were BSI (24 cases; 41.4%), hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) (11 cases; 19.0%), and HAP/VAP plus BSI (10 cases; 17.2%). Combo therapy was used in 22 out of 58 cases (37.9%), including fosfomycin (n = 16), tigecycline (n = 4), or gentamycin (n = 2, nebulized in one case), and was maintained for the overall treatment duration. Details of patients receiving combo therapy are shown in Table S1.

A total of 122 ceftazidime-avibactam therapeutic drug monitoring (TDM) were performed, with a median (IQR) of 2 (1–2) assessments per patient. The median (IQR) time of the first TDM assessment was 3 (2–5) days, and that of subsequent TDM assessments was 6 (5–8) days. The median (IQR) ceftazidime fC_{ss}/MIC ratio and avibactam

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TABLE 1 Demographics and clinical characteristics of patients treated with CI ceftazidime-avibactam targeted therapy[a]

Variables	Overall included patients (*n* = 58)
Demographics	
Age (median [IQR])	62.5 (55.5–73.8)
Gender (male/female; *n* [%])	36/22 (62.1/37.9)
Body mass index (median [IQR])	24.7 (22.2–28.4)
Baseline eGFR (mL/min/1.73 m^2; median [IQR])	86.5 (41.3–109.8)
ICU admission (*n* [%])	31 (53.4)
Augmented renal clearance (*n* [%])	6 (10.3)
Continuous renal replacement therapy (*n* [%])	15 (25.9)
Immunosuppression (*n* [%])	16 (27.6)
Underlying disease (*n* [%])	
Severe COVID-19	8 (13.8)
Febrile neutropenia	8 (13.8)
Hepatic cirrhosis	8 (13.8)
Solid organ transplantation	8 (13.8)
Bowel perforation	6 (10.3)
Acute cholecystitis	4 (6.9)
Cancer	3 (5.2)
Other	13 (22.4)
Site of infection	
BSI	24 (41.4)
HAP/VAP	11 (19.0)
HAP/VAP + BSI	10 (17.2)
IAI + BSI	7 (12.1)
IAI	3 (5.2)
SSTI	1 (1.7)
CNS	1 (1.7)
CNS + BSI	1 (1.7)
CAZ-AVI treatment	
Initial full maintenance dosing (*n* [%])	54 (93.1)
Length of treatment (days; median [IQR])	13.5 (7.75–19)
Combination therapy	22 (37.9)
Ceftazidime fC_{ss}/MIC ratio (median [IQR])	23.5 (13.4–39.1)
Avibactam fC_{ss}/C_T ratio (median [IQR])	3.5 (2.2–6.2)
PK/PD joint target attainment (*n* [%])	
Optimal	53 (91.4)
Quasi-optimal	4 (6.9)
Suboptimal	1 (1.7)
Outcome	
Microbiological eradication	53 (91.4)
Clinical cure	46 (79.3)
Resistance development	2 (3.4)
30-day mortality rate	15 (25.9)

[a]BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CI, continuous infusion; CNS, central nervous system; C_T, threshold concentration; eGFR, estimated glomerular filtration rate; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; PK/PD, pharmacokinetic/pharmacodynamic; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia.

fC_{ss}/C_T ratio were 23.5 (13.4–39.1) and 3.5 (2.2–6.2), respectively. Dosing adjustments were recommended in 25/58 cases (43.1%), with 20 decreases (34.5%) and 5 increases (8.6%). Details of the implemented ceftazidime-avibactam dosing adjustments are shown in Table S2. The joint PK/PD target of ceftazidime-avibactam was optimal in 53 out of 58 cases (91.4%), quasi-optimal in 4 cases (6.9%), and suboptimal in 1 case (1.7%).

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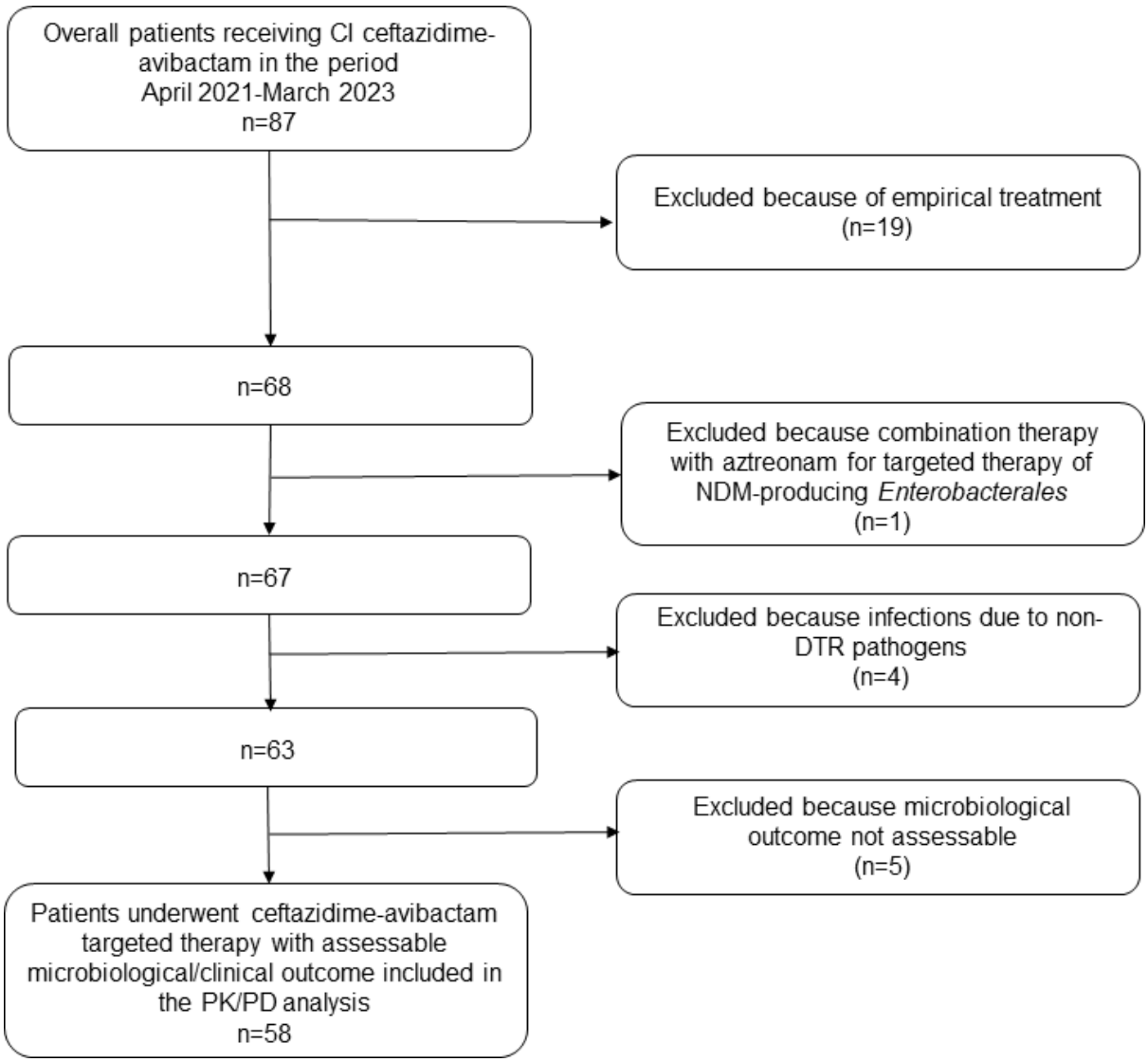

FIG 1 Flowchart of patient inclusion and exclusion criteria for PK/PD analysis.

Among the 22 patients receiving combo therapy, data on PK/PD target attainment of the concomitant agents were available for 13 out of the 16 patients who were co-treated with fosfomycin, being optimal in 11/13 cases (84.6%; Table S1). Microbiological eradication was documented in 53/58 patients (91.4%), clinical cure was documented in 79.3% of cases, resistance to ceftazidime-avibactam occurred in 2/58 cases (3.4%), and the overall 30-day mortality rate was 25.9%.

Univariate analysis of patients receiving ceftazidime-avibactam mono- vs combo therapy is shown in Table 2. Combo therapy was administered more frequently to patients who were ICU admitted (72.7% vs 41.7%; $P = 0.023$) or affected by HAP/VAP (40.9% vs 5.6%; $P = 0.001$) and less frequently to those affected by IAI plus BSI (19.4% vs 0.0%; $P = 0.04$). The proportion of patients with optimal PK/PD target attainment of CI ceftazidime-avibactam was similar between the two groups (88.9% vs 95.5%; $P = 0.64$), and combo therapy did not grant any significant benefit compared to monotherapy in terms neither of microbiological eradication (90.9% vs 91.7%; $P = 0.99$) nor of clinical cure (81.8% vs 77.8%; $P = 0.99$), resistance occurrence (4.5% vs 2.8%; $P = 0.99$), and 30-day mortality rate (36.4% vs 19.4%; $P = 0.16$).

Univariate and multivariate regression analyses testing the variables possibly associated with the microbiological outcome are shown in Table 3. Overall, in the

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TABLE 2 Univariate analysis comparing patients receiving mono- vs combo therapy with CI CAZ-AVI for targeted therapy of DTR Gram-negative infections[a]

Variables	Monotherapy (*n* = 36)	Combination therapy (*n* = 22)	*P* value
Demographics			
Age (median [IQR])	62 (54.75–72.5)	63 (58.75–75.25)	0.39
Gender (male/female; *n* [%])	20/16 (55.6/44.4)	16/6 (72.7/27.3)	0.19
Body mass index (median [IQR])	23.9 (21.0–28.0)	26.3 (23.7–29.5)	0.12
Baseline eGFR (mL/min/1.73 m^2; median [IQR])	88.0 (46.0–110.0)	81.0 (32.7–103.0)	0.43
ICU admission (*n* [%])	15 (41.7)	16 (72.7)	0.023
Continuous renal replacement therapy (*n* [%])	8 (22.2)	7 (31.8)	0.42
Augmented renal clearance (*n* [%])	5 (13.9)	1 (4.5)	0.39
Site of infection (*n* [%])			
BSI	18 (50.0)	6 (27.3)	0.09
HAP/VAP	2 (5.6)	9 (40.9)	0.001
HAP/VAP + BSI	7 (19.4)	3 (13.7)	0.73
IAI + BSI	7 (19.4)	0 (0.0)	0.04
IAI	1 (2.8)	2 (9.1)	0.55
SSTI	0 (0.0)	1 (4.5)	0.38
CNS + BSI	1 (2.8)	0 (0.0)	0.99
CNS	0 (0.0)	1 (4.5)	0.38
Pathogens (*n* [%])			
KPC-producing *K. pneumoniae*	14 (38.9)	4 (18.2)	0.14
DTR *P. aeruginosa*	7 (19.4)	7 (31.8)	0.29
OXA-48-producing *K. pneumoniae*	5 (14.0)	7 (31.8)	0.18
OXA-48-producing *Escherichia coli*	3 (8.3)	1 (4.5)	0.99
Carbapenem-resistant *Klebsiella aerogenes* (non-CPE)	3 (8.3)	1 (4.5)	0.99
Carbapenem-resistant *K. pneumoniae* (non-CPE)	3 (8.3)	0 (0.0)	0.28
KPC/OXA-48-coproducing *K. pneumoniae*	0 (0.0)	2 (9.1)	0.14
AmpC-producing *Enterobacter cloacae*	1 (2.8)	0 (0.0)	0.99
PK/PD joint target attainment (*n* [%])			
Optimal	32 (88.9)	21 (95.5)	0.64
Quasi-optimal/suboptimal	4 (11.1)	1 (4.5)	0.64
Outcome (*n* [%])			
Microbiological eradication	33 (91.7)	20 (90.9)	0.99
Clinical cure	28 (77.8)	18 (81.8)	0.99
Resistance occurrence	1 (2.8)	1 (4.5)	0.99
30-day mortality rate	7 (19.4)	8 (36.4)	0.16

[a]BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CNS, central nervous system; CPE, carbapenemase-producing *Enterobacterales*; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; PK/PD, pharmacokinetic/pharmacodynamic; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia.

multivariate analysis, suboptimal/quasi-optimal joint PK/PD target attainment of CI ceftazidime/avibactam was the only independent predictor of microbiological failure (odds ratio [OR] 11.11; 95% confidence interval [CI] 1.31–93.98; $P = 0.027$), whereas monotherapy was not ($P = 0.99$).

Figure 2 depicts the microbiological outcomes of DTR Gram-negative infections among patients receiving CI ceftazidime-avibactam mono- (panel A) or combo therapy

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TABLE 3 Univariate and multivariate analyses comparing patients showing microbiological eradication vs microbiological failure[a]

Variables	Microbiological eradication (*n* = 53)	Microbiological failure (*n* = 5)	Univariate analysis *P* value	Multivariate analysis (OR; 95% CI)	Multivariate analysis *P* value
Demographics					
Age (median [IQR])	63.0 (55.0–74.0)	60.0 (57.0–61.0)	0.26		
Gender (male/female; *n* [%])	34/19 (64.2/35.8)	2/3 (40.0/60.0)	0.36		
Body mass index (median [IQR])	24.7 (22.2–28.6)	23.1 (20.8–27.5)	0.40		
Baseline eGFR (mL/min/1.73 m^2; median [IQR])	85.0 (38.9–107.0)	120.0 (84.5–124.0)	0.18		
ICU admission (*n* [%])	28 (52.8)	3 (60.0)	0.99		
Continuous renal replacement therapy (*n* [%])	14 (26.4)	1 (20.0)	0.99		
Augmented renal clearance (*n* [%])	4 (7.5)	2 (40.0)	0.08		
Site of infection (*n* [%])					
BSI	24 (45.3)	0 (0.0)	0.07		
HAP/VAP	9 (17.0)	2 (40.0)	0.24		
HAP/VAP + BSI	9 (17.0)	1 (20.0)	0.99		
IAI + BSI	5 (9.4)	2 (40.0)	0.11		
IAI	3 (5.6)	0 (0.0)	0.99		
SSTI	1 (1.9)	0 (0.0)	0.99		
CNS + BSI	1 (1.9)	0 (0.0)	0.99		
CNS	1 (1.9)	0 (0.0)	0.99		
Pathogens (*n* [%])					
KPC-producing *K. pneumoniae*	16 (30.2)	2 (40.0)	0.64		
DTR *P. aeruginosa*	13 (24.5)	1 (20.0)	0.99		
OXA-48-producing *K. pneumoniae*	11 (20.7)	1 (20.0)	0.99		
OXA-48-producing *E. coli*	4 (7.5)	0 (0.0)	0.99		
Carbapenem-resistant *K. aerogenes* (non-CPE)	3 (5.7)	1 (20.0)	0.31		
Carbapenem-resistant *K. pneumoniae* (non-CPE)	3 (5.7)	0 (0.0)	0.99		
KPC/OXA-48-coproducing *K. pneumoniae*	2 (3.8)	0 (0.0)	0.99		
AmpC-producing *E. cloacae*	1 (1.9)	0 (0.0)	0.99		
CAZ-AVI treatment and PK/PD joint target attainment (*n* [%])					
Quasi-optimal/suboptimal joint PK/PD target attainment	3 (5.7)	2 (40.0)	0.05	11.11 (1.31–93.98)	0.027
Combination therapy	20 (37.7)	2 (40.0)	0.99		

[a]BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; CNS, central nervous system; CPE, carbapenemase-producing *Enterobacterales*; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; PK/PD, pharmacokinetic/pharmacodynamic; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia.

(panel B) in relation to the optimal or suboptimal/quasi-optimal joint PK/PD target attainment, type of infection, and causative pathogen. Overall, BSI accounted for 41.4% of infections, and KPC-Kp (18 cases; 31.0%), OXA-48-producing *Enterobacterales* (16 cases; 27.6%), and DTR-PA (14 cases; 24.1%) accounted for more than three-quarters of the causative pathogens. All of the clinical isolates were fully susceptible to ceftazidime-avibactam, with an MIC value ranging from 0.5 to 8 mg/L. Microbiological failure occurred in 5/58 cases (8.6%). Three out of five occurred among patients with optimal joint PK/PD target attainment (two receiving combo therapy, one for treating VAP due to DTR-PA and the other for treating BSI plus VAP caused by OXA-48-producing Kp; the other one receiving monotherapy for treating IAI plus BSI), and the other two occurred among those with suboptimal/quasi-optimal PK/PD target attainment (both receiving monotherapy, one for treating IAI plus BSI due to KPC-Kp and the other one for treating VAP due to carbapenem-resistant *K. aerogenes*).

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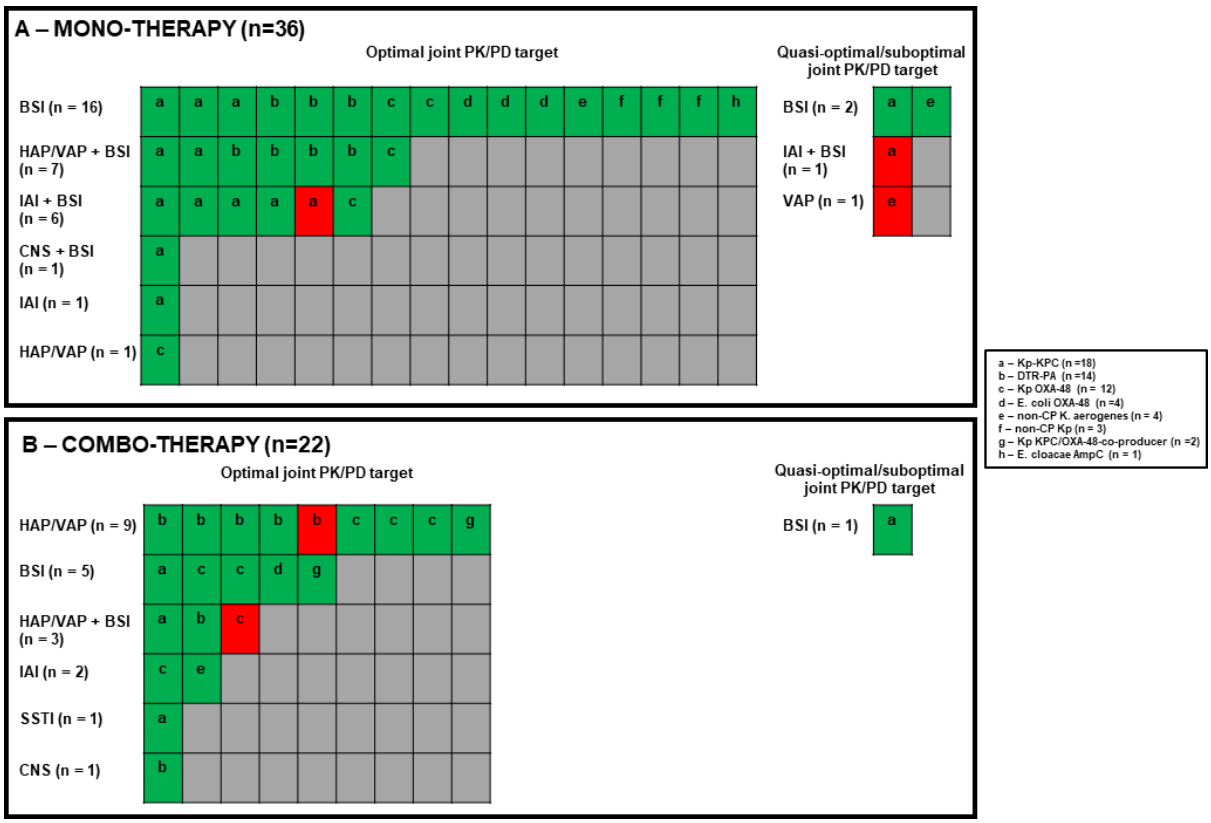

FIG 2 Relationship between pharmacokinetic/pharmacodynamic joint target attainment and the microbiological outcome in patients treated with CI ceftazidime-avibactam monotherapy (A) or combination therapy (B) for documented DTR Gram-negative infections. Green box, microbiological eradication; red box, microbiological failure; gray box, absence of a specific type of infection. Each cell corresponds to a single patient. BSI, bloodstream infection; CNS, central nervous system; DTR-PA, difficult-to-treat resistant *P. aeruginosa*; HAP, hospital-acquired pneumonia; IAI, intrabdominal infection; Kp, *K. pneumoniae*; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia.

DISCUSSION

To the best of our knowledge, this is the first study that explored by multivariate regression analysis the relationship between the joint PK/PD target of CI ceftazidime-avibactam and the microbiological outcome in a cohort of patients with documented DTR Gram-negative infections. Our findings suggest that suboptimal/quasi-optimal joint PK/PD target attainment of CI ceftazidime/avibactam was the only independent risk factor associated with microbiological failure, whereas monotherapy was not, and that the TDM-guided approach allowed optimal joint PK/PD target attainment in the vast majority of cases.

Ceftazidime-avibactam is a first-line therapy in the management of severe infections caused by several KPC-Kp or OXA-48-producing *Enterobacterales* and/or by some DTR-PA (12, 13). Several authors nowadays argue about the need to use it in combo therapy when treating deep-seated DTR Gram-negative infections (14). This was especially suggested for HAP/VAP, considering that when using standard infusion over 2 h, the penetration rate of around 30% in the epithelial lining fluid (ELF) might cause suboptimal exposure at the infection site (3, 15).

Even in our study, combination therapy was used mainly in critically ill patients with HAP/VAP caused by DTR-PA or OXA-48-producing *Enterobacterales*, and fosfomycin was the agent most frequently combined. However, our findings showed once more that combo therapy was not associated with better microbiological/clinical outcomes, in agreement with what was previously shown in other real-world studies (4, 16).

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Conversely, in our study, optimal joint PK/PD target attainment of CI ceftazidime-avibactam was the only predictor significantly associated with microbiological eradication of DTR Gram-negative infections, irrespective of the infection site and/or of the type of DTR Gram-negative causative pathogens. Shields and co-workers found that among 77 patients receiving ceftazidime-avibactam for treating CRE infections, the clinical failure rate was associated with pneumonia (P = 0.045), and they attributed this to potential suboptimal exposure at the infection site (3). Interestingly, Tumbarello et al. found in turn that lower respiratory tract infections were associated with increased mortality (P = 0.04) among 577 adults treated with ceftazidime-avibactam for KPC-Kp infections, although they also showed that prolonged infusion administration resulted in reduced mortality (P = 0.006) (4). In this regard, CI administration, as we did, may favor even more aggressive and stable PK/PD target attainment at the infection site with better microbiological and/or clinical outcomes compared with intermittent infusion (5, 17). This may support the contention that optimizing joint PK/PD target attainment of CI ceftazidime-avibactam monotherapy may represent an effective way of enabling microbiological eradication.

TDM of both ceftazidime and avibactam plasma concentrations coupled with expert interpretation and eventual dosing adaptation should represent the only way effective for assessing properly the relationship between PK/PD target attainment and the microbiological or clinical outcome (18). Some previous real-world studies measured only TDM of ceftazidime C_{ss} for assessing the relationship between PK/PD target attainment of CI ceftazidime-avibactam and the clinical outcome (19, 20) and simply presumed that avibactam C_{ss} were effective without measuring them (19, 20). However, it should not be overlooked that nowadays measuring avibactam concentrations could be the best way for optimizing ceftazidime-avibactam therapy, since some preclinical and clinical studies showed that increasing avibactam concentrations may have a key role in maximizing clinical efficacy and in preventing resistance occurrence in patients receiving ceftazidime-avibactam (8, 9). That is why we introduced the concept of a joint PK/PD target and measured both ceftazidime and avibactam concentrations for optimizing properly ceftazidime-avibactam therapy. This concept was applied first in a descriptive manner to two small case series of critically ill patients with DTR Gram-negative infections (10, 11). The findings of this cohort study may further strengthen the contention that optimal joint PK/PD target attainment of CI ceftazidime-avibactam may be a valuable approach for granting microbiological eradication even with monotherapy. Suboptimal and/or quasi-optimal ceftazidime-avibactam joint PK/PD target attainment emerged as an independent risk factor of microbiological failure and was in agreement with what was previously reported for both traditional (7, 21–23) and novel beta-lactams (24). Overall, the findings may support the valuable role that a TDM-guided strategy focused on promptly optimizing joint PK/PD target attainment of CI ceftazidime-avibactam may have in minimizing the risk of microbiological failure and of resistance development in the targeted monotherapy of DTR Gram-negative infections.

We recognize that our study has some limitations. The retrospective monocentric study design should be acknowledged. The reliability of multivariate regression analysis might have been potentially hampered by the small sample size of patients having microbiological failure. The majority but not all of the patients with combo therapy had the PK/PD target attainment of the combo-agent assessed. Being of 2 the median of ceftazidime-avibactam TDM assessments per patient, the fact that PK/PD targets remained optimal throughout all treatment duration could only be assumed. However, it is unlikely that the pathophysiological conditions could have affected these findings considering the more than optimal PK/PD target attainment observed in the vast majority of cases. Total ceftazidime and avibactam concentrations were measured, and the free moieties were only estimated based on plasma protein binding retrieved in the literature without applying any adjustment based on the patient-specific plasma protein levels. However, considering the limited plasma protein binding of both agents, the potential impact of hypoalbuminemia was expected to be negligible.

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In conclusion, our findings suggest that optimizing joint PK/PD target attainment of CI ceftazidime-avibactam monotherapy could represent a way forward for allowing microbiological eradication in the targeted treatment of DTR Gram-negative infections. Larger prospective studies are warranted to confirming our findings.

MATERIALS AND METHODS

We performed a retrospective cohort study including adult patients who, in the period between 1 April 2021 and 31 March 2023, were admitted at the IRCCS Azienda Ospedaliero-Universitaria of Bologna, Italy, were treated in mono- or combo therapy with CI ceftazidime-avibactam because of documented DTR Gram-negative infections, and underwent at least one TDM of both ceftazidime and avibactam. Patients receiving empirical treatment and/or having microbiological outcomes not assessable were excluded.

Demographic (age, sex, and body mass index) and clinical/laboratory data (ward of admission, underlying diseases, baseline creatinine clearance, occurrence of ARC, need for CRRT, site/type of infection, clinical isolate and MIC of ceftazidime/avibactam, mono- or combo therapy, and treatment duration) were retrieved for each patient.

Types of infection were defined according to standard criteria. Isolation of a DTR Gram-negative from at least one blood culture was defined as BSI; that from the bronchoalveolar lavage fluid culture with a bacterial load of $\geq 10^4$ CFU/mL or from the endotracheal aspirate with a bacterial load of $\geq 10^6$ was defined as documented HAP, if occurring after >48 h from hospital admission, or as documented VAP, if occurring after >48 h from endotracheal intubation and start of mechanical ventilation; that from the peritoneal fluid culture was defined as documented intra-abdominal infection (IAI); that from a biopsied sample of the advancing margin skin lesion was defined as documented skin and soft tissue infection (SSTI); and that from the cerebrospinal fluid (CSF) culture was defined as documented central nervous system (CNS) infection (25, 26).

Broth microdilution (panel provided by Merlin Diagnostika GmbH, Bornheim-Hersel, Germany) was used for testing ceftazidime-avibactam susceptibility. Tested MIC values of ceftazidime ranged from 1 to 64 mg/L in the presence of a fixed target avibactam concentration (C_T) of 4 mg/L and were interpreted according to the EUCAST guidelines (27). Resistance to ceftazidime-avibactam was defined as an MIC value of ceftazidime >8 mg/L in the presence of an avibactam C_T of 4 mg/L. The multiplex immunochromatographic assay NG-Test CARBA 5 (NG Biotech, Guipry-Messac, France) was implemented for detecting the specific carbapenemase type (i.e., IMP, VIM, NDM, KPC, and OXA-48) produced by DTR Gram-negative isolates.

Ceftazidime-avibactam therapy was always started with a loading dose of 2.5 g over a 2-h infusion, and the initial maintenance dose (MD) was selected case-by-case based on renal function. The selected MD was 2.5 g q8h over 8 h (namely by CI) in patients with normal renal function and 1.25–0.625 g q8h over 8 h in those with moderate (creatinine clearance 31–50 mL/min/1.73 m^2) or severe renal dysfunction (creatinine clearance ≤30 mL/min/1.73 m^2). Ceftazidime-avibactam aqueous solutions were reconstituted every 8 h and infused over 8 h due to stability restrictions (28).

Blood samples for TDM of ceftazidime and avibactam C_{ss} were collected first after at least 24 h from starting therapy and then reassessed whenever feasible. Total ceftazidime and avibactam plasma concentrations were measured according to a validated liquid chromatography-tandem mass spectrometry method, as previously described (29). Only total ceftazidime and avibactam concentrations were measured, and the free fractions (*f*) were calculated by multiplying by 0.90 and 0.93 the total ceftazidime and avibactam C_{ss}, respectively (based on the reported 10% and 7% plasma protein binding of ceftazidime and avibactam, respectively) (30, 31). The just previously described joint PK/PD target of ceftazidime-avibactam was selected as PD parameter efficacy (10). It was defined as optimal when both the fC_{ss}/MIC ratio of ceftazidime was ≥4 (equivalent to 100% $fT_{>4xMIC}$) and the fC_{ss}/C_T ratio of avibactam was >1 (equivalent to 100%

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*f*T >C_T of 4.0 mg/L) and as quasi-optimal or suboptimal if only one or none of the two were attained, respectively. TDM-based ceftazidime-avibactam dosing adjustments were provided whenever needed, as previously reported (6, 32).

Microbiological failure was defined as persistence of the pathogen at the infection site after more than 7 days from starting ceftazidime-avibactam treatment (3). Resistance development was defined as an MIC increase of ceftazidime-avibactam against the clinical isolate beyond the EUCAST clinical breakpoint of susceptibility. The primary outcome was microbiological eradication, defined as the absence of the index pathogen from the primary site of infection in at least two subsequent assessments. Secondary outcomes were as follows: clinical cure, defined as complete resolution of signs and symptoms of the infection coupled with documented microbiological eradication at the end of treatment and the absence of recurrence or relapse at 30-day follow-up (33); ceftazidime-avibactam resistance development; and 30-day mortality rate.

Continuous data were presented as median and IQR, whereas categorical variables were expressed as count and percentage. Univariate analysis between patients receiving mono- or combo therapy was performed by means of Fisher's exact test or the chi-squared test (for categorical variables) or the Mann-Whitney *U* test (for continuous variables). Multivariate logistic regression analysis was implemented for testing possible variables associated with microbiological failure. Independent covariates with a *P* value < 0.10 in the univariate analysis were included in the multivariate logistic regression model. Statistical significance was defined as a *P* value < 0.05. Statistical analysis was performed by means of MedCalc for Windows (MedCalc statistical software, version 19.6.1, MedCalc Software Ltd., Ostend, Belgium). The study was approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (n. 442/2021/Oss/AOUBo approved on 28 June 2021).

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AUTHOR CONTRIBUTIONS

Milo Gatti, Conceptualization, Data curation, Formal analysis, Writing – original draft | Matteo Rinaldi, Data curation | Cecilia Bonazzetti, Data curation | Paolo Gaibani, Data curation | Maddalena Giannella, Writing – review and editing | Pierluigi Viale, Conceptualization, Writing – review and editing | Federico Pea, Conceptualization, Writing – review and editing

ETHICS APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria of Bologna (n. 442/2021/Oss/AOUBo approved on 28 June 2021).

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Supplementary Tables (AAC00969-23-S0001.docx). Supplementary Tables 1 and 2.

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