Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by *Enterobacteriales* Coresistant to Carbapenems and Polymyxins

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ABSTRACT In this article, we report a case series of patients with infections caused by *Enterobacteriales* coresistant to carbapenems and polymyxins who were treated with ceftazidime/avibactam (CAZ-AVI) salvage therapy on a compassionate-use protocol. We enrolled 29 adult patients in 3 centers that had an infection due to a resistant microorganism and for whom the treatments available were considered ineffective, treated them with CAZ-AVI, and assessed clinical and microbiological cure at the end of treatment and all-cause mortality at 14 days and 30 days. The antimicrobial susceptibility profile was determined using broth microdilution, and total genomic DNA was sequenced. Twelve (41.4%) patients had bacteremia, and 48.3% (14/29) of the infections were treated with combination therapy. All strains were producers of KPC-2 and were susceptible to CAZ-AVI (MIC₉₀, 1 µg/ml). Clinical success was high (24/29 [82.7%; 95% confidence interval, 64.2 to 94.2%]), even for the bacteremic cases (75%). The 14-day and 30-day mortality rates were 9/29 (31%) and 15/29 (51.7%), respectively. The 14-day mortality rate for pneumonia was the same as that for bloodstream infections (33.3%) and although not significant, we found that patients with renal impairment that received adjusted doses of CAZ-AVI had high mortality (4/9 [44%]; *P* = 0.22). We concluded that CAZ-AVI is an option for the treatment of severe infections due to difficult-to-treat drug-resistant *Enterobacteriales*.

KEYWORDS CRE, *Enterobacteriales*, KPC-Kp, extensively drug resistant

KPC-2-producing *Klebsiella pneumoniae* (KPC-Kp) isolates were first reported in Brazil in 2009 (1). Since then, this pathogen has spread and become endemic in Brazilian hospitals. According to the last report of the Brazilian Health Surveillance Agency (ANVISA), *K. pneumoniae* ranked as the second most frequent pathogen, causing 3,085 (18.2%) bloodstream infections (BSI) in adult intensive care units in 2016. Unfortunately, 46.8% of *K. pneumoniae* isolates reported to ANVISA were resistant to carbapenems (2).

High mortality rates have been attributed to KPC-Kp infections worldwide (3). In addition, KPC-Kp isolates are usually multidrug resistant with very few therapeutic options. Although there has been a debate over whether combination therapy would be superior to monotherapy, no prospective, randomized controlled trial has yet been completed. Evidence gathered from retrospective or nonrandomized prospective cohorts of clinically heterogeneous populations suggests that combination therapy may offer a survival benefit compared to monotherapy for treatment of KPC-Kp infections (3,

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4). Infections due to polymyxin-resistant KPC-Kp (Pol-R KPC-Kp) isolates have been reported worldwide, with polymyxin-resistant isolates being reported as independent predictors of 14-day mortality (5). The percentage of Pol-R KPC-Kp has dramatically increased in Brazil from 0% to 27.1% between the years 2011 and 2015 (6).

Ceftazidime-avibactam (CAZ-AVI) is a new cephalosporin- β -lactamase inhibitor combination approved for the treatment of complicated urinary tract and intra-abdominal infections and nosocomial pneumonia and other serious Gram-negative infections (7). Recently, Tumbarello and collaborators retrospectively studied 138 cases of KPC-Kp infections treated with CAZ-AVI as salvage therapy. These authors have documented that the 30-day mortality rate of bacteremic patients who received CAZ-AVI was lower than that for patients treated with other antimicrobials (8). Although this study evaluated the efficacy of CAZ-AVI in a large number of patients, no microbiological data including susceptibility to polymyxins were reported.

We report a case series of patients with infections caused by KPC-2-producing *Enterobacteriales* coresistant to carbapenems and polymyxins who were treated with CAZ-AVI as salvage therapy on a compassionate-use protocol. Although CAZ-AVI was recently approved in Brazil, it has not become commercially available yet. To our knowledge, this is the first study to evaluate the use of CAZ-AVI for polymyxin-resistant infections.

RESULTS

We enrolled 29 patients; 18 (62%) were male, and the mean age was 50.5 years. All patients had some underlying disease, and 11 (37.9%) were considered immunocompromised due to transplantation or hematological disorders. Most patients (17/29 [58.6%]) were hospitalized in intensive care units. The types of infection were primary BSI (12 [41.4%]), urinary tract infection (UTI) (8 [27.6%]), intra-abdominal infection (IAI) (4 [13.8%]), nosocomial pneumonia (NP) (3 [10.3%]), and complicated skin and soft tissue infection (SSTI) (2 [6.9%]). The mean hospital length of stay was 66.7 days. The duration of treatment ranged from 4 to 19 days (mean, 11.8 days), excluding two outliers—one patient who received only 2 days of treatment and died due to the severity of illness and another patient who received 24 days of treatment due to a necrotizing fasciitis. Seventeen patients (58.6%) had previous use of antimicrobial agents, with a median duration of 8 days. Meropenem and colistin were the antimicrobial agents prescribed. CAZ-AVI was the initial therapy for 12 patients (41.4%) and was initiated a median of 37 days after hospital admission. Patients were included in the protocol a median of 35 days after hospital admission, ranging from 2 to 106 days, and 24/29 patients (82.7%) had more than 10 days of hospitalization. Fourteen patients (48.2%) received combination therapy. The antimicrobial regimens prescribed and the clinical and microbiological characteristics are described in Table 1.

Clinical cure was observed in 24 patients (82.7%). Microbiological response was evaluated only in BSI infections (12 patients), and all of them had cure, even those who died. Only 33.3% (4/12) of the bacteremic patients died. Of those, only one patient died within the first 6 days after diagnosis. He had a carbapenem-resistant *Serratia marcescens* BSI with Pitt and Charlson scores of 3 and 2, respectively. The 14-day all-cause mortality rate for BSI was the same as that for pneumonia (1/3 [33.3%]). Only one patient with pneumonia died. He was a severely immunosuppressed patient with AIDS and a Charlson score of 4. The 14-day and 30-day all-cause mortality rates were 31.0% and 51.7%, respectively. The mean number of days between initial therapy and death was 13.6.

Nine of fourteen (64.2%) patients with impaired renal function received adjusted doses of CAZ-AVI. While no fatalities were noticed for the five patients (35.8%) who did not receive an adjusted dosage, four of nine patients (44%) who received a CAZ-AVI adjusted dosage, died ($P = 0.22$). These patients were diagnosed with BSI (two patients) and NP and SSTI (one patient each). Regarding the 14-day mortality, three patients who received combination therapy died (3/14 [21.4%]), compared to six patients (6/15 [40%]) in the monotherapy group ($P = 0.21$); the difference was not statistically significant. Four (13.7%) adverse reactions were observed, diarrhea (not associated with

TABLE 1 Clinical and microbiological characteristics of 29 patients with KPC-2-producing *Enterobacteriales* infections treated with compassionate use of CAZ-AVI

Characteristics	Value
Demographic characteristics	
Age in yrs, mean	50, 5
Male gender, no. (%)	18 (62)
Comorbidities	
No. with renal impairment (%)	14 (48.2)
No. with transplant (%)	7 (24.1)
No. with hematologic disorder (%)	4 (13.7)
No. with hepatic insufficiency (%)	2 (6.9)
Site of infection	
No. with primary bloodstream infection (%)	12 (41.4%)
No. with urinary tract infection (%)	8 (27.6%)
No. with intra-abdominal infection (%)	4 (13.8%)
No. with nosocomial pneumonia (%)	3 (10.3%)
No. with skin and soft tissue infection (%)	2 (6.9%)
Median Charlson score (range)	2 (0–5)
No. with Charlson score ≥ 3 (%)	4 (21.1)
Median Pitt score no. (range) ($n = 12$)	2 (0–8)
Pitt score ≥ 4 , no. (%) ($n = 12$)	2 (16.6)
CAZ-AVI treatment	
Mean days of treatment (range)	12 (2–24)
No. with concurrent antibiotic treatment (%)	14 (48.3)
Tigecycline + polymyxin	3 (21.4)
Tigecycline + polymyxin + meropenem	2 (14.2)
Polymyxin	2 (14.2)
Meropenem	2 (14.2)
Polymyxin + tigecycline + amikacin + meropenem	1 (7.1)
Polymyxin + amikacin	1 (7.1)
Amikacin + tigecycline	1 (7.1)
Gentamicin	1 (7.1)
Fosfomycin (oral)	1 (7.1)
Outcomes	
No. of clinical cure (%)	24 (82.7)
No. of microbiological response (%)	12 (41.3)
No. of 14-day mortality (%)	9 (31.0)
No. of 30-day mortality (%)	15 (51.7)
No. of adverse events (%)	4 (13.7)
Microbiological results by antimicrobial susceptibility testing (AST) + WGS	
<i>K. pneumoniae</i> ($n = 20$)	
MLST (no.)	ST258 (9), ST11 (7), ST16 (4)
MIC ₉₀ (range) in $\mu\text{g/ml}/\%$ susceptible	
Colistin	>8 (1–8)/90%
CAZ/AVI	1 (0.12–4)/100%
Resistance-encoding genes	
β -lactamases (no.)	<i>bla</i> _{KPC-2} (20), <i>bla</i> _{CTX-M-2} (3), <i>bla</i> _{CTX-M-14} (9), <i>bla</i> _{CTX-M-15} (3), <i>bla</i> _{OXA-2} (4), <i>bla</i> _{TEM-1B} (10), <i>bla</i> _{SHV-1} (2), <i>bla</i> _{SHV-11} (16), <i>bla</i> _{SHV-148-like} (2)
Porins	
No. of <i>ompK35</i> mutations	20
No. of <i>ompK36</i> mutations	20
Colistin	
No. of <i>pmrB</i> mutation (R256G)	15
No. of <i>phoP</i> mutation (H14Q)	1
No. of <i>mgrB</i> mutation/disruption	13
Aminoglycosides	
No. of aminoglycoside-modifying enzymes	<i>aac</i> (3)-IIa (7), <i>aac</i> (3)-IIc (3), <i>aac</i> (3)-IId (5), <i>aac</i> (6')-Ib (12), <i>aac</i> (6')IIb-cr (9), <i>aac</i> A4 (3), <i>aad</i> A2 (11), <i>aad</i> A4, <i>aph</i> (3')-Ia (7), <i>aph</i> (3'')-Ib (9), <i>aph</i> (6)-Id (9)
No. of 16S ribosomal RNA methyltransferases	<i>rmtB</i> (9)
No. of fosfomycin	<i>fosA</i> (20)
<i>S. marcescens</i> ($n = 1$)	
CAZ/AVI MIC ($\mu\text{g}/\text{mc}$)	0.12 (susceptible)
Resistance-encoding genes	<i>bla</i> _{SRT-2} , <i>bla</i> _{OXA-9} , <i>bla</i> _{KPC-2} , <i>aadA</i> , <i>aac</i> (6')-Ic, <i>fosA</i> , <i>qnrB27</i>

Clostridioides difficile) in two patients and one episode each of cutaneous rash and gastrointestinal bleeding.

A total of 30 carbapenem-resistant Gram-negative bacilli (28 *K. pneumoniae* and 2 *S. marcescens*) were isolated from 29 patients. Of those, 20 *K. pneumoniae* isolates and 1 *S. marcescens* isolate were available for further microbiological characterization (Table S1 in the supplemental material). All tested isolates were susceptible to CAZ-AVI, with MICs ranging from 0.12 to 4 $\mu\text{g/ml}$ (MIC_{90} , 1 $\mu\text{g/ml}$). In contrast, all *K. pneumoniae* isolates were resistant to aztreonam (MIC_{90} , >128 $\mu\text{g/ml}$), ceftazidime (MIC_{90} , 128 $\mu\text{g/ml}$), cefepime (MIC_{90} , >16 $\mu\text{g/ml}$), meropenem (MIC_{90} , >8 $\mu\text{g/ml}$), and piperacillin-tazobactam (MIC_{90} , >128 $\mu\text{g/ml}$). *bla*_{KPC-2} was detected in all isolates. In addition, the extended-spectrum β -lactamase (ESBL)-encoding genes *bla*_{CTX-M-2}, *bla*_{CTX-M-14}, and *bla*_{CTX-M-15} were identified, respectively, in *K. pneumoniae* isolates belonging to sequence type 11 (ST11) (3 of 7 isolates), ST16 (3 of 4 isolates), and ST258 (9 of 9 isolates). Moreover, all isolates showed mutations on genes encoding the OmpK35 and OmpK36 porins. Eighteen *K. pneumoniae* isolates were coresistant to polymyxin (MIC_{90} , >8 $\mu\text{g/ml}$) with *pmrB* mutations (R256G; 15 isolates) and *mgrB* mutations (W20S; 6 isolates) or disruption (7 isolates), which were the most common mechanisms of polymyxin resistance. In contrast, tigecycline was the most active agent *in vitro* (MIC_{90} , 1 $\mu\text{g/ml}$; 90.0% susceptible), followed by amikacin (MIC_{90} , >32 $\mu\text{g/ml}$; 50% susceptible). Nine *K. pneumoniae* ST258 isolates from two distinct hospitals harbored *rmtB1*, which encodes a 16S rRNA methylase. In addition, multiple aminoglycoside-modifying enzyme-encoding genes were also present in our collection. Fortunately, the *S. marcescens* isolate was susceptible to levofloxacin (MIC, 2 $\mu\text{g/ml}$) and tigecycline (MIC, 0.5 $\mu\text{g/ml}$).

DISCUSSION

Carbapenem-resistant *K. pneumoniae* isolates, especially due to the production of KPC-2, represent an important public health problem with a high burden to the Brazilian health care system. In this study, we report our initial real-life experience with CAZ-AVI in treating 29 patients diagnosed with severe infections caused by difficult-to-treat *Enterobacteriales*. All isolates harbored *bla*_{KPC-2} and, except for one, were identified as *K. pneumoniae*. Importantly, these bacterial isolates were highly resistant, with 26 of 29 (89.7%) being resistant to polymyxin B. Three KPC-KP isolates were susceptible to polymyxins, but patients infected by these isolates failed previous polymyxin therapy and for this reason were included in the compassionate study. Why did these three patients fail polymyxin therapy? We evaluated these patients separately and found that they were all hematologic patients diagnosed with acute leukemia who were neutropenic when diagnosed with BSI. Therapeutic failure may be related to host factors. Fortunately, all of these patients survived, making CAZ-AVI a therapeutic option in this specific population. Most studied KPC-KP isolates were grouped under clonal complex 258 (CC258) (ST258 and ST11), which has been reported as the most frequent CC and is responsible for spread of KPC in Brazil (9). Curiously, we observed the spread of the KPC-KP ST16 clone within two hospitals located in the city of São Paulo.

Despite our patients being severely ill (58.6% at the ICU, 48.3% with moderate-to-severe renal impairment, and 48% with hypotension at the time of diagnosis) and BSI and NP being considered severe infections with high mortality rates, a high rate of clinical success at the end of therapy (82.7%) was observed with CAZ-AVI. It has been reported that the clinical success rate of CAZ-AVI therapy against KPC-Kp infections was higher than those observed for other antimicrobial agents (85% versus 70.0%) (10). In another CAZ-AVI compassionate study, 68.4% of all patients and 69.2% of those who had bacteremia showed clinical cure, with an in-hospital mortality of 42.3% (11).

In our study, the 14-day all-cause mortality rate was 31%. The rate was slightly higher in patients diagnosed with BSI (33.3%). The analysis of the 14-day mortality rate was chosen because it had a higher chance of being attributed to the infection episode. Our 30-day all-cause mortality was higher (51.7%) than those previously documented by Tumbarello and collaborators (34.1%) considering that these patients had received the best therapy available when this study was performed (8).

We did not find a correlation with worse outcome in patients diagnosed with pneumonia as Shields and collaborators reported, but in patients with renal impairment requiring dosage adjustment, we found a higher mortality rate (12). Due to the small number of patients enrolled in this study, the observed differences did not reach statistical significance in our analysis. The small number of patients included is the major limitation of our study, but even so, we were able to include 29 patients in this compassionate use protocol. The fact that this study was a compassionate protocol also enabled the use of combination therapy according to medical decisions. Although combination therapy did not reach a statistically significant difference for 14-day mortality, there are still many doubts about combination therapy with CAZ-AVI in order to improve outcomes, and more studies are needed. Another doubt concerns dose adjustment for patients with renal impairment. Is there a need for adjustment? The manufacturer recommends adjustment, but as demonstrated by Shields, patients with renal failure had worse outcomes perhaps due to inadequate doses to achieve therapeutic efficacy (12).

Despite this fact, patients treated with CAZ-AVI showed better clinical outcomes and lower mortality and side effect rates. For these reasons, we conclude that CAZ-AVI is an important addition to the therapeutic armamentarium against extensively drug-resistant *Enterobacteriales*, including strains resistant to carbapenems and polymyxins. Due to the increasing numbers of reports of CAZ-AVI resistance, we urge prudent use to maintain its effectiveness for as long as possible (13).

MATERIALS AND METHODS

Patients. We prospectively enrolled adults admitted at three tertiary teaching hospitals located in southeast Brazil from August 2016 to May 2018 that met inclusion criteria. The inclusion criteria were (i) patients older than 18 years-old and (ii) patients with complicated urinary tract infection (UTI), intra-abdominal infection (IAI), or nosocomial pneumonia (NP) due to confirmed *Enterobacteriales*. Complicated urinary tract infection was defined as an infection that occurred in a urinary tract with structural or functional abnormalities or that developed in a hospital environment; intra-abdominal infection was defined as an infection extending beyond the hollow viscera to the peritoneal cavity and was associated with the presence of abscess or peritonitis; nosocomial pneumonia was defined as the appearance of pulmonary infiltrates together with the onset of fever, purulent sputum, leukocytosis, and decreased oxygenation that developed 48 hours after hospital admission.

Patients with bloodstream infections (BSI) could be included in the study only if they had failed or reported serious adverse reaction to current antimicrobial therapy. Therapeutic failure was considered if the patient had persistent positive blood cultures after 3 days of antimicrobial therapy, and an adverse reaction was considered if the patient had any condition that contraindicated the use of available therapies. All patients included in the analysis needed to have received at least 2 days of therapy with CAZ-AVI, and the drug was prescribed at the dose of 2.5 g by 2-h intravenous infusion every 8 h. Dosages were adjusted for patients with moderate or severe renal impairment according to the instructions of the manufacturer's package insert (14).

The main outcome variables were clinical cure at the end of treatment, microbiological response at the end of treatment, and 14-day and 30-day all-cause mortality rates. Clinical cure was classified as improved signs and symptoms from baseline to the end of therapy with defervescence based on information entered in the medical records. The protocol allowed the concomitant use of other antimicrobials according to the doctor's opinion due to the limited options for treatment.

Microbiological response was classified as a negative culture at the same site as basal culture after treatment. The Pitt bacteremia score and Charlson comorbidity index were evaluated to predict mortality and were assessed on the day of the positive culture.

Results were expressed as mean or median (continuous variables) or as percentages of the group from which they were derived (categorical variables). Despite the small sample size, comparisons between groups for 14-day all-cause mortality were made using Fisher's exact or chi-square tests for categorical variables. The study was approved by both local and national ethics committees. All patients or family members signed the study informed consent.

Microbiological characterization. Species identification and susceptibility testing were initially performed at routine microbiology laboratories and confirmed at a research laboratory using matrix-assisted laser desorption/ionization–time of flight mass spectrometry (MALDI-TOF MS) with a Microflex low-throughput (LT) mass spectrometer and Biotyper version 3.3 software (Bruker Daltonics, Bremen, Germany). The antimicrobial susceptibility profile was determined using broth-microdilution and interpreted according to EUCAST recommendations (15). *Enterobacteriales* was considered resistant to carbapenem if the MIC for meropenem was >8 mg/ml. In brief, total genomic DNA was sequenced using an Illumina MiSeq platform (Illumina Inc., San Diego, CA). Genome assembly was performed using Newbler version 3.0. The System for Automated Bacterial Integrated Annotation (SABIA) pipeline and the NCBI Prokaryotic Genome Annotation Pipeline PROKKA version 3.2 (<http://www.vicbioinformatics.com/software/prokka.shtml>) were both applied for automatic annotation and gene prediction followed by manual validation. Multilocus sequence type (MLST) and resistance genes were screened using MLST

version 2.0 (<https://cge.cbs.dtu.dk/services/MLST/>) and ResFinder version 3.1 (<https://cge.cbs.dtu.dk/services/ResFinder/>).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.00528-19>.

SUPPLEMENTAL FILE 1, XLSX file, 0.03 MB.

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