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Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms: a case series from the compassionate-use program

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Department of Epidemiology and Preventive Medicine, Tel Aviv Sourasky Medical Center,	11
Tel Aviv, Israel <sup>a</sup> ; Department of Infectious Diseases, Hospital Universitario Reina Sofía,	12
Córdoba, Spain <sup>b</sup> ; Instituto Maimónides de Investigación Biomédica, Universidad de	13
Cordoba, Córdoba, Spain <sup>c</sup> ; Department of Infectious Disease, University Medical Center	14
Ljubljana, Ljubljana, Slovenia <sup>d</sup> ; Infectious Diseases Unit, Department of Medicine, Hospital	15
de la Santa Creu i Sant Pau, Barcelona, Spain <sup>e</sup> ; Institut d'Investigació Biomèdica Sant Pau,	16
Universitat Autònoma de Barcelona, Barcelona, Spain <sup>f</sup> ; Infectious Diseases Unit, Department	17
of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna,	18
Bologna, Italy <sup>g</sup> ; Department of Clinical Microbiology, Hospital Universitario de Gran	19
Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain <sup>h</sup> ; Department of Infectious	20
Diseases, St Vincent's Hospital, Melbourne, Australia <sup>i</sup> ; Infectious Diseases Unit, Hospital	21
Universitario La Paz-IdiPAZ, Madrid, Spain <sup>j</sup> ; Critical Care Department, Hospital Clínico San	22
Carlos, Madrid, Spain <sup>k</sup> ; Department of Infectious Diseases, Hospital Clínic, IDIBAPS,	23
Barcelona University, Barcelona, Spain <sup>l</sup> ; Infectious Diseases Department, Hospital Ramón y	24
Cajal, Madrid, Spain <sup>m</sup> ;	25

Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel,	26
Switzerland <sup>n</sup> ; Department of Critical Care Medicine, Hospital Universitario Reina Sofia,	27
Córdoba, Spain <sup>o</sup> ; Department of Medical Surgical Sciences, Alma Mater Studiorum	28
University of Bologna, Bologna, Italy <sup>p</sup> ; Centre Hospitalier Universitaire Bichat-Claude	29
Bernard, AP-HP, Paris, France <sup>q</sup> ; Université Paris Diderot University, Paris, France <sup>r</sup> ;	30
Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel <sup>s</sup>	31
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**Abstract** 38

Ceftazidime-avibactam (CAZ-AVI) is a recently approved  $\beta$ -lactam  $\beta$ -lactamase inhibitor 39  
combination with the potential to treat serious infections caused by carbapenem-resistant 40  
organisms. Few patients with such infections were included in the CAZ-AVI clinical trials, 41  
and clinical experience is lacking. We present a case series of patients with infections caused 42  
by carbapenem-resistant Enterobacteriaceae (CRE) or *Pseudomonas aeruginosa* (CRPa) who 43  
were treated with CAZ-AVI salvage therapy on a compassionate-use basis. Physicians who 44  
had prescribed CAZ-AVI completed a case report form. We used descriptive statistics to 45  
summarize patient characteristics and treatment outcomes. We used Wilcoxon rank-sum and 46  
Fisher's exact tests to compare patients by treatment outcome. The sample included 36 47  
patients with CRE and two with CRPa. The most common infections were intra-abdominal 48  
and respiratory. Physicians categorized 60.5% of patients as having life-threatening 49  
infections. All but two patients received other antibiotics before CAZ-AVI, for a median of 50  
13 days. The median duration of CAZ-AVI treatment was 16 days. Twenty-five patients 51  
(65.8%) concurrently received other antibiotics to which their pathogen was non-resistant *in* 52  
*vitro*. Twenty-eight patients (73.7%, 95% CI; 56.9-86.6%) experienced clinical and/or 53  
microbiological cure. Five patients (20.8%) with documented microbiological cure died, 54  
whereas 10 patients (71.4%) with no documented microbiological cure died ( $p=0.01$ ). In 55  
three-quarters of cases, CAZ-AVI (alone or combined with other antibiotics) cured infections 56  
caused by carbapenem-resistant organisms, 95% of which had failed previous therapy. 57  
Microbiological cure was associated with improved survival. CAZ-AVI shows promising 58  
clinical results for infections for which treatment options are limited. 59

60

<b>Introduction</b>	61
Ceftazidime-avibactam (CAZ-AVI), a $\beta$ -lactam $\beta$ -lactamase inhibitor combination, was	62
approved by the US Food and Drug Administration (FDA) in February 2015 (1). It is	63
indicated for the treatment of complicated urinary tract infection (cUTI) and complicated	64
intra-abdominal infection (cIAI) (in combination with metronidazole) in adults with limited	65
or no other therapeutic options. A promising characteristic of CAZ-AVI is its potential to	66
treat infections caused by carbapenem-resistant Enterobacteriaceae (CRE) or carbapenem-	67
resistant <i>Pseudomonas aeruginosa</i> (CRPa). Avibactam recovers the activity of ceftazidime	68
by inhibiting Ambler Class A, Class C and some Class D beta-lactamases, including the KPC	69
and OXA-48 carbapenemases; CAZ-AVI is not active against metallo- $\beta$ -lactamases (MBLs)	70
such as NDM, IMP and VIM (2, 3). In an <i>in vitro</i> study that included 276 meropenem-	71
nonsusceptible <i>Klebsiella</i> spp. isolates, 98.9% were susceptible to CAZ-AVI (4). In a second	72
study, 67.4% of 396 meropenem-nonsusceptible <i>P. aeruginosa</i> isolates were susceptible to	73
CAZ-AVI (5). A third study reported 100% susceptibility to CAZ-AVI among 133 non-	74
carbapenemase producing Enterobacteriaceae isolates in which the mechanism of	75
carbapenem resistance was extended-spectrum beta-lactamase (ESBL) and/or AmpC	76
production together with porin deficiency (6).	77
Clinical data on the efficacy of CAZ-AVI against carbapenem-resistant organisms in humans	78
are scarce. In Phase II trials (7, 8) and recently completed Phase III trials (9, 10) of CAZ-	79
AVI to treat cUTI and cIAI, the comparator drug was a carbapenem; therefore, patients with	80
infections caused by carbapenem-resistant organisms were excluded. In a pathogen- directed	81
open-label Phase III trial ("REPRISE") comparing CAZ-AVI to best available therapy for	82
treatment of cUTI and cIAI caused by ceftazidime-resistant Gram-negative organisms (11),	83
few patients with carbapenem-resistant infections met the trial's inclusion criteria. Among	84
the 292 Enterobacteriaceae recovered from 288 patients in the REPRISE trial, only nine	85

harbored non-MBL carbapenemases: six KPC-producing *K. pneumoniae*, and three OXA-48-  
producing *K. pneumoniae* (12). In an effort to amass data about the effectiveness of CAZ-  
AVI against carbapenem-resistant organisms, we present a case series of patients with  
infections caused by CRE or CRPa who were treated with CAZ-AVI salvage therapy on a  
compassionate-use basis. Our primary aim was to evaluate three outcomes: clinical cure at  
the end of treatment, microbiological cure at the end of treatment, and all-cause in-hospital  
mortality. Our secondary aim was to identify predictors of cure and of survival.

## Materials and Methods

**Data collection.** When data for this paper were collected, CAZ-AVI was not approved for  
use in the European Union. Upon our request, AstraZeneca (a co-developer of CAZ-AVI)  
contacted physicians to whom they had provided compassionate access CAZ-AVI to treat  
carbapenem-resistant infections, and invited them to participate in the study. AstraZeneca  
had no further involvement. Twenty-five physicians agreed to participate and were sent case  
report forms. To be eligible for inclusion, patients must have received at least one dose of  
CAZ-AVI in the context of compassionate use. Data collected included patient demographic  
characteristics, co-morbidities and McCabe score (13), a description of the infection treated  
by CAZ-AVI (including an antibiogram), treatment with other antibiotics before or  
concurrently with CAZ-AVI, reasons for using CAZ-AVI, details of CAZ-AVI treatment,  
adverse events, the clinical and microbiological response, and relapse of infection.

**Microbiological methods.** Each hospital conducted antibiotic susceptibility testing according  
to its own protocols. We report susceptibility as it was interpreted by the local laboratories.  
All sites tested for susceptibility to CAZ-AVI by disk diffusion; results were interpreted  
according to the breakpoints set by the FDA (14). Plasma concentrations of ceftazidime and  
avibactam were not assessed during the course of treatment.

**Statistical methods.** The main outcome variables were clinical response at the end of treatment, microbiological response at the end of treatment, and all-cause in-hospital mortality. Clinical response was classified as cure, partial improvement, or treatment failure resulting in death and was analyzed as cure vs. partial improvement or treatment failure. Microbiological response was classified as a negative culture, positive culture, or culture not repeated and was analyzed as documented cure (negative culture) vs. positive culture or culture not repeated. Patient characteristics measured as continuous variables were summarized by median and interquartile range; categorical variables were summarized as proportions. The McCabe score was treated as a dichotomous variable, with a score > 1 indicating underlying disease with death expected within 5 years. Patient characteristics were compared by outcome using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables. Analyses were performed in Stata version 13 (Stata Corporation, College Station, Texas).

**Results**

**Sample.** Of the 25 physicians contacted, 17 responded and 15 contributed at least one patient with an infection caused by CRE or CRPa sensitive to CAZ-AVI, for a total of 38 patients. Included patients had been treated in Europe and Australia in the years 2013-2016. Fifteen patients came from a single hospital in Spain that had an outbreak of KPC-producing *K. pneumoniae*; the characteristics of this strain have been previously described (15). Thirty-six patients (94.7%) received CAZ-AVI as salvage therapy after treatment with other antibiotics had failed; in the other two patients, CAZ-AVI was the first antibiotic chosen because no other appropriate treatment was available. Three patients were treated at institutions where CAZ-AVI clinical trials were conducted, but were treated on a compassionate-use basis because they met the trial's exclusion criteria.

**Organisms.** Thirty-four patients were infected with *Klebsiella pneumoniae*, one with *Klebsiella oxytoca*, one with *Escherichia coli* and two with *P. aeruginosa*. Antimicrobial susceptibilities are presented in Table 1. All but one isolate were classified by the local laboratories as resistant to imipenem. In the patient with an imipenem-susceptible carbapenamase-producing organism (OXA-48-producing *E. coli*), treatment with imipenem had resulted in microbiological failure. All isolates were resistant to ceftazidime alone, with minimum inhibitory concentrations (MICs) ranging from 8 to  $\geq 64$   $\mu\text{g/mL}$ . Only 14 of 34 isolates tested (41.2%) were susceptible to colistin. Table 2 summarizes the MICs of carbapenems in the 33 isolates for which carbapenem susceptibility was reported quantitatively. One patient with KPC-producing *K. pneumoniae* with an imipenem MIC of  $<2$  and a meropenem MIC of 2 had failed treatment with a multidrug regimen that included meropenem; carbapenem treatment was not tried in the other two patients with imipenem MICs of 2. Exact results of disk diffusion testing for CAZ-AVI susceptibility were available for all but five isolates, with zone diameters ranging from 21 to 32 mm for Enterobacteriaceae and from 20 to 23 mm for *P. aeruginosa*. (FDA breakpoints are 21 mm and 18 mm, respectively [14])

**Patient characteristics and prior treatment.** Patients' demographic and clinical characteristics are shown in Table 3. All but two patients had received antibiotics before CAZ-AVI (median=3 drugs) and had failed treatment. Among those who received prior antibiotics, the median duration of treatment before CAZ-AVI was started was 13 days. The most commonly prescribed agents were tigecycline (n=26), meropenem (n=18), gentamicin (n=16), fosfomycin (n=14), and colistin (n=11).

**CAZ-AVI treatment.** Characteristics of CAZ-AVI treatment are presented in Table 3. The minimum length of treatment was 3 days. Twenty-four patients (63.2%) were given the

standard dose of CAZ-AVI throughout their treatment (ceftazidime 2 g /avibactam 0.5 g every 8 hours). Fourteen patients with renal impairment received adjusted doses. Twenty-five patients (65.8%) were treated concurrently with at least one other antibacterial to which their organism was non-resistant *in vitro*; the most common agents were tigecycline (n=11), amikacin (n=9), and fosfomycin (n=4).

**Outcomes.** Treatment outcomes are presented in the Figure. Twenty-eight patients (73.7%, 95% CI: 56.9-86.6%) experienced clinical and/or documented microbiological cure at the end of treatment. All-cause in-hospital mortality was 39.5% (95% CI: 24.0-56.6%). Ten patients died during their hospitalization because of treatment failure, such that infection-related mortality was 26.3% (95% CI: 13.4-43.1%). Among these ten patients, the median time from the start of CAZ-AVI treatment to death was 19 days (IQR: 7-31 days). Six of them were still receiving CAZ-AVI within one day of their death. Nine of the 13 patients (69.2%) who received CAZ-AVI as monotherapy achieved clinical and/or microbiological cure, compared to 19 out of 25 patients (76.0%) given a concurrent antibiotic with *in vitro* activity against their pathogen (p=0.71).

For three of the four patients with documented microbiological failure, the repeat positive isolates were tested for susceptibility to CAZ-AVI; none had developed CAZ-AVI resistance. Two patients with documented microbiological cure of infections caused by KPC-producing *K. pneumoniae* experienced a relapse, one at 16 days and the other at 30 days after the end of both CAZ-AVI treatment and discharge from the hospital. In the first case, the isolate remained susceptible to CAZ-AVI by disk diffusion testing and the patient experienced clinical and microbiological cure of the relapse infection following dual therapy with CAZ-AVI and gentamicin. In the second case, the relapse isolate was not tested for CAZ-AVI susceptibility; repeat CAZ-AVI treatment was not considered because of the patient's poor

prognosis, and the patient died 73 days after infection onset of causes not directly related to the infection.

Table 4 presents treatment outcomes according to infection site. Among the 38 patients there were 46 infections, not including secondary bacteremia. Eighteen of the 46 infections (39.1%) were either cIAI or cUTI, indications for which CAZ-AVI was approved; 13 patients had only cIAI or cUTI, with or without bacteremia. All-cause mortality was 14.3% in patients with primary or central-line associated bacteremia and 42.3% in patients with any bacteremia. Five out of 24 patients (20.8%) with documented microbiological cure died (of causes unrelated to the infection), whereas 10/14 patients (71.4%) with no documented microbiological cure died ( $p=0.01$ ).

Table 5 compares characteristics of patients by treatment outcome. Patients treated for a longer time with other antibiotics prior to CAZ-AVI administration were less likely to experience clinical cure ( $p=0.06$ ) and microbiological cure ( $p=0.01$ ). Among patients infected with Enterobacteriaceae, survival was higher in patients with KPC carbapenemase as compared to OXA-48: 17/23 patients (73.9%) with KPC-producing organisms survived until discharge, compared to 5/13 patients (38.5%) with OXA-48 producers ( $p=0.07$ ). These 2 groups of patients did not differ by the proportion with life-threatening infection ( $p=0.73$ ) or high McCabe score ( $p=0.50$ ). Neither of the two cases of relapse occurred in patients with OXA-48; one of the four cases of documented microbiological failure occurred in a patient with OXA-48.

Six patients (15.8%) developed adverse events that were attributed to CAZ-AVI. Blood alkaline phosphatase increased in two patients; nausea/vomiting, *Clostridium difficile*-associated diarrhea, convulsions, and disorientation progressing to stupor occurred in one patient each.

<b>Discussion</b>	206
The proportion of Gram-negative infections caused by carbapenem-resistant strains is	207
increasing. According to US surveillance systems, carbapenem resistance in nosocomial	208
infections caused by <i>Klebsiella spp.</i> rose from 1.6% in 2001 to 10.4% in 2011 (16). Regional	209
differences in resistance are striking: in the 2014 report of the EARS-Net European	210
surveillance system, the proportion of <i>Klebsiella spp.</i> isolated from blood or cerebrospinal	211
fluid that was carbapenem-resistant ranged from 0.0% in Norway, Sweden, Finland and	212
Estonia to 62.3% in Greece (17).	213
Treatment options for carbapenem-resistant organisms are limited; they primarily include	214
colistin, aminoglycosides, tigecycline (for CRE only), fosfomycin, and double-carbapenem	215
therapy. A recent systematic review by Falagas et al. of 20 non-randomized studies	216
compared mortality following different antibiotic regimens for CRE infections (18).	217
Mortality was variously defined as 28- or 30-day, in-hospital, infection-related, or	218
unspecified. Mortality associated with the most common treatment regimens was up to 57%	219
for colistin alone, up to 80% for tigecycline alone, up to 64% for colistin-tigecycline, up to	220
50% for gentamicin-tigecycline, and up to 67% for combined therapy with colistin and a	221
carbapenem. While colistin has been considered the mainstay of therapy for carbapenem-	222
resistant infections (19), colistin resistance among CRE has increased (20). In our study, 59%	223
of tested isolates were colistin resistant. Although we lack information about the laboratory	224
methods used at each study site, and some methods for colistin susceptibility testing are	225
flawed (with inaccurate results more likely to be false-susceptible than false-resistant) (21),	226
these test results are relevant because they influenced the decision to use CAZ-AVI. The	227
rationale behind double-carbapenem therapy for carbapenem-resistant organisms is that	228
ertapenem, which is more easily hydrolyzed by carbapenemases, saturates these enzymes so	229
that higher concentrations of the second carbapenem are available to treat the infection. Two	230

recent articles summarized the outcomes of 29 patients who received double-carbapenem therapy for infections caused by carbapenem-resistant *K. pneumoniae*; clinical success was achieved in 16 cases (55%) (22, 23).

In our study, 73.7% of patients with infections caused by CRE or CRPa who received salvage therapy with CAZ-AVI experienced clinical and/or microbiological cure, and all-case in-hospital mortality was 39.5%. Among those cured were patients with infections at difficult-to-treat sites, such as endocarditis and osteomyelitis, for which CAZ-AVI has not been studied. Mortality among patients with bacteremia was 42%. In previous studies, all-cause mortality from CRE bacteremia ranged from 19% (among patients given combination therapy that included a carbapenem) to 94% (24-29). In our study, microbiological cure was a predictor of survival: 79% of patients with negative cultures at the end of treatment survived until discharge. Among the 21% of patients who achieved microbiological cure but did not survive, mortality was attributed to other, non-infection-related causes. The delayed onset of CAZ-AVI treatment was associated with worse clinical and microbiological outcomes. Minimizing CAZ-AVI use in order to prevent the emergence of resistance is critical; however, waiting to exhaust all other (and potentially more toxic) treatment options before resorting to CAZ-AVI may reduce a patient's likelihood of being cured.

We found that having an infection caused by an OXA-48-producing pathogen, as opposed to a KPC-producing pathogen, was a predictor of mortality; the association did not reach statistical significance ( $p=0.07$ ), likely because of the small sample size. OXA-48 does not hydrolyze ceftazidime efficiently and does not usually cause ceftazidime resistance. However, most OXA-48 producing isolates are resistant to ceftazidime due to co-production of ESBL enzymes (30). Because ESBLs are well inhibited by avibactam and OXA-48 is partly inhibited by avibactam (31), the higher mortality observed in patients infected with

OXA-48 producers is unexpected and intriguing. We do not have further details on the strains that can shed light on this finding, and further studies are warranted.

Shields et al. recently published a single-center case series of 37 patients with CRE infections treated with CAZ-AVI for at least 3 days (32). In contrast to our study, in which 95% of patients received CAZ-AVI as salvage therapy, CAZ-AVI was the first drug used to treat CRE infections in Shields' study. CAZ-AVI was administered as monotherapy in 70% of patients. Fifty-nine percent of patients experienced clinical success, defined as survival without recurrence at 30 days, clinical improvement, and negative cultures within 7 days of the start of treatment. Thirty-day all-cause mortality was 24%. Because of differences in how outcomes were defined, the results of Shields' study and ours are not directly comparable. Notably, three patients in Shields' study developed CAZ-AVI resistance following 10-19 days of treatment. A study of KPC-producing Enterobacteriaceae demonstrated the *in vitro* selection of CAZ-AVI-resistant mutants, primarily via alterations to the bla<sub>KPC</sub>  $\Omega$  loop (33). In our study, when CAZ-AVI susceptibility testing was repeated in 1/2 patients with relapse of infection and 3/4 patients with documented microbiological failure, no resistance was detected.

We found two additional clinical studies of CAZ-AVI treatment for carbapenem-resistant infections. . The first was a case report of a 64 year-old woman who received compassionate-use CAZ-AVI for bacteremia caused by KPC-producing *K. pneumoniae* that did not respond to colistin and dual-carbapenem therapy. She was treated successfully with CAZ-AVI and ertapenem (23). The second was a case series of three patients (aged 72 to 89) with CRE bacteremia that did not respond to previous antibiotics. All three achieved clinical and microbiological cure following monotherapy with CAZ-AVI (34).

In our case series there were six adverse events that were attributed to CAZ-AVI, three of which were severe. One patient who received CAZ-AVI in combination with two other antibiotics developed *C. difficile* infection during treatment. Like nearly all antibiotics, CAZ-AVI alters the normal flora of the colon, predisposing patients to *C. difficile* infection, as has been shown in healthy volunteers given CAZ-AVI (35). The risk of *C. difficile* infection following CAZ-AVI treatment appears to be low: only three of 1,204 (0.2%) patients treated with CAZ-AVI in three Phase III clinical trials developed *C. difficile* infection (9-11). There were two neurological adverse events in our case series: convulsions and disorientation with progression to stupor. While it is not clear if these events were related to CAZ-AVI use or to other factors, the neurotoxic effects of cephalosporins are described mostly in the elderly and in patients with renal impairment or prior neurologic disease (36). Both patients in our study who developed neurotoxicity were aged 70 or over, with normal renal function.

The main limitation of this study, as with any case series, is the lack of a concurrent control group; comparison is to the published experience summarized above. Comparison to a concurrent control group is problematic because of the potential for selection bias, confounding by indication, and confounding by time to treatment. A second limitation is that the experience with CAZ-AVI in the context of compassionate use may not be generalizable to the population of patients who may be candidates for CAZ-AVI treatment. Patients in compassionate use programs often have severe acute illness or co-morbidities that make them ineligible for clinical trials, increasing their risk of adverse outcomes (37). On the other hand, a sample of such patients may be biased toward clinical success: physicians may be more likely to request compassionate-use drugs for patients with a favorable underlying diagnosis, and immortal time bias may be present, as patients need to survive long enough for the drug to arrive. A third limitation is that two-thirds of patients received CAZ-AVI concurrently with other antibiotics with *in vitro* activity against their pathogen. In these patients, it is

difficult to ascertain whether the clinical success was associated with CAZ-AVI, the  
 concurrent antibiotic, or the combination of both. However, when we compared patients who  
 received CAZ-AVI monotherapy to those who were given additional antibiotics, the  
 proportion cured was similar; thus, we believe CAZ-AVI had a major role in the cure.  
 Finally, the small sample size may have precluded us from identifying significant predictors  
 of clinical cure, microbiological cure, and mortality.

In summary, we presented a case series of patients treated with CAZ-AVI for carbapenem-  
 resistant infections on a compassionate-use basis. The majority of patients had life-  
 threatening infections, some in difficult-to-cure sites, and 95% of them had failed previous  
 antibiotic treatments. Three-quarters of patients experienced clinical and/or microbiological  
 cure following CAZ-AVI treatment. CAZ-AVI shows promising clinical results for  
 infections for which treatment options are extremely limited.

<b>Authors' contributions</b>	315
ET and YC were responsible for the study design, literature search, data analysis, and writing	316
of the article. All other authors contributed cases to the case series, assisted with data	317
analysis and writing, and reviewed the manuscript.	318
<b>Conflict of interests</b>	319
AstraZeneca provided the list of physicians who contributed cases to this study; AstraZeneca	320
did not initiate, design, or fund this study, nor was it involved in data analysis or writing of	321
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NB has received honoraria from AstraZeneca for development of educational presentations,	323
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YC has received funds from AstraZeneca in the form of consulting fees, research grants, and	325
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Table 1. Antimicrobial susceptibility of isolates from patients with carbapenem-resistant  
infections treated with compassionate-use CAZ-AVI

Antibiotic	Number of isolates tested <sup>a</sup>	% Susceptible
Imipenem	36	2.8% <sup>b</sup>
Meropenem	33	0.0%
Ceftazidime	38	0.0%
Colistin	34	41.2%
Gentamicin	37	51.4%
Amikacin	38	31.6%
Tigecycline	32	62.5%
Fosfomycin	29	55.2%

<sup>a</sup>Isolates included 34 *K. pneumoniae*, 1 *K. oxytoca*, 1 *E. coli*, 2 *P. aeruginosa*

<sup>b</sup>Patient with OXA-48-producing *E. coli* who had failed imipenem treatment (MIC not reported)

Table 2. Minimum inhibitory concentrations (MICs) of carbapenems in 33 isolates for which  
susceptibility was reported quantitatively

Organism-antibiotic	MIC			
	<2 (n)	2 (n)	4-8 (n)	>8 (n)
Enterobacteriaceae - imipenem (n=29)	1	2	2	24
Enterobacteriaceae -meropenem (n=27)	0	1	2	24
<i>P. aeruginosa</i> - imipenem (n=2)	0	0	0	2
<i>P. aeruginosa</i> -meropenem (n=1)	0	0	0	1

Table 3. Characteristics of patients with carbapenem-resistant infections treated with  
compassionate-use CAZ-AVI

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Characteristic	Patients (N=38)
<b>Demographic characteristics</b>	
Age in years, median (IQR)	61 (47-67)
Male sex	25 (65.8%)
Location before hospitalization	
Home	33 (86.8%)
Transferred from another hospital	5 (13.2%)
Co-morbidities	
Transplant recipient	5 (13.2%)
Diabetes mellitus	8 (21.1%)
Immunosuppression <sup>a</sup>	10 (26.3%)
Renal disease	7 (18.4%)
Cardiovascular disease	11 (28.9%)
McCabe score >1	19 (50.0%)
<b>Infection characteristics</b>	
Organism and carbapenemase	
<i>Klebsiella pneumoniae</i>	
KPC	22
OXA-48	12
<i>Klebsiella oxytoca</i> (KPC)	1
<i>Escherichia coli</i> (OXA-48)	1
<i>Pseudomonas aeruginosa</i>	2
Hospital-acquired infection	34 (89.5%)
Bacteremia	26 (68.4%)
Polymicrobial infection	11 (29.0%)
Life-threatening infection (high risk of death within 30 days)	23 (60.5%)
<b>Antibiotics before CAZ-AVI</b>	
Received antibiotics before CAZ-AVI for this infection	36 (94.7%)
Days of antibiotic treatment before CAZ-AVI, median (IQR)	13 (7-31)
Number of antibiotics before CAZ-AVI, median (IQR)	3 (3-4)
<b>Other treatments before CAZ-AVI</b>	
Surgery to remove the source of infection	16 (42.1%)
Removal of foreign body involved in infection	9 (23.7%)
<b>Clinical status at start of CAZ-AVI treatment</b>	
Mechanical ventilation	14 (36.8%)
Vasopressor support	17 (44.7%)
Unconscious	12 (31.6%)
<b>CAZ-AVI treatment</b>	

Days of treatment, median (IQR)	16 (14-21)	
Extended infusion	36 (94.7%)	
Concurrent antibiotic treatment <sup>b</sup>	25 (65.8%)	
Received standard CAZ-AVI dose	24 (63.2%)	503

<sup>a</sup>Immunosuppression was defined as post-transplant, chemotherapy in past 6 weeks, systemic steroids (> 20 mg of prednisone) or other immunosuppressive agents in past 2 weeks, absolute neutrophil count of < 500 /μL, or HIV/AIDS 504

<sup>b</sup>During CAZ-AVI treatment, patient received another antibiotic to which organism was non-resistant *in vitro* 507

IQR: interquartile range 509

Table 4 Outcomes of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI, by infection site

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Infection site <sup>a</sup>	Number of cases	Cases with bacteremia	Life-threatening infection	Documented microbiological cure	Clinical cure		In-hospital death		Mortality among patients with microbiological cure	
					N (%)	95% CI	N (%)	95% CI	N (%)	95% CI
All patients	38	26 (68 4%)	23 (60 5%)	24 (63 2%)	26 (68 4%)	51 3%-82 5%	15 (39 5%)	24 0%-56 6%	5 (20 8%)	7 1%-42 2%
Intra-abdominal	15	11 (73 3%)	8 (53 3%)	6 (40 0%)	10 (66 7%)	38 4%-88 2%	6 (40 0%)	16 3%-67 7%	1 (16 7%)	0 4%-64 1%
Pneumonia <sup>b</sup>	7	6 (85 7%)	5 (71 4%)	3 (42 9%)	3 (42 9%)	9 9%-81 6%	5 (71 4%)	29 0%-96 3%	1 (33 3%)	0 8%-90 6%
Skin and soft tissue	4	3 (75 0%)	1 (25 0%)	1 (25 0%)	1 (25 0%)	0 6%-80 6%	2 (50 0%)	6 8%-93 2%	0 (0 0%)	0 0%-97 5%
Urinary tract	3	2 (66 7%)	1 (33 3%)	2 (66 7%)	2 (66 7%)	9 4%-99 2%	2 (66 7%)	9 4%-99 2%	1 (50%)	1 3%-98 7%
Primary or catheter-associated bacteremia	7	7 (100%)	7 (100%)	7 (100 0%)	7 (100%)	59 0%-100%	1 (14 3%)	0 4%-57 9%	1 (14 3%)	0 4%-57 9%
Any bacteremia	26	26 (100%)	20 (76 9%)	18 (69 2%)	18 (69 2%)	48 2%-85 7%	11 (42 3%)	23 4%-63 1%	4 (22 2%)	6 4%-47 6%
Endocarditis	2	1 (50 0%)	1 (50 0%)	2 (100 0%)	2 (100 0%)	15 8%-100%	1 (50 0%)	1 3%-98 7%	1 (50%)	1 3%-98 7%
Osteomyelitis	3	0 (0 0%)	0 (0 0%)	2 (66 7%)	2 (66 7%)	9 4%-99 2%	1 (33 3%)	0 8%-90 6%	0 (0 0%)	0 0%-84 2%
Surgical site infection	2	1 (50 0%)	2 (100%)	1 (50 0%)	1 (50 0%)	1 3%-98 7%	1 (50 0%)	1 3%-98 7%	0 (0 0%)	0-97 5%
Other <sup>c</sup>	3	1 (33 3%)	2 (66 7%)	3 (100%)	2 (66 7%)	9 4%-99 2%	1 (33 3%)	0 8%-90 6%	1 (33 3%)	0 8%-90 6%

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<sup>a</sup>Patients may have multiple infection sites

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<sup>b</sup>Pneumonia cases included 6 cases of ventilator-associated pneumonia and 1 case of hospital-acquired pneumonia

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<sup>c</sup>Other infection types (1 patient each) were ventriculitis/subdural abscess, prosthetic joint infection, and mucositis

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Table 5 Comparison of characteristics of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI, by treatment outcome

Characteristic	Clinical cure			Documented microbiological cure			Survival to hospital discharge		
	yes n=26	no n=12	p-value	yes n=24	no n=14	p-value	yes n=23	no n=15	p-value
Age in years, median (IQR)	54 (46-65)	62 (58-69)	0.25	63 (48-70)	58 (46-63)	0.41	54 (47-66)	61 (44-68)	0.68
Male sex	17 (65.4%)	8 (66.7%)	1.00	14 (58.3%)	11 (78.6%)	0.29	16 (69.6%)	9 (60.0%)	0.73
McCabe score > 1	14 (53.9%)	5 (41.7%)	0.73	14 (58.3%)	5 (35.7%)	0.31	12 (52.2%)	7 (46.7%)	1.00
Days of antibiotic treatment before CAZ-AVI, median (IQR)	9 (5-17)	21 (10-50)	0.06	8 (3-16)	29 (11-45)	0.01	10 (5-20)	15 (6-31)	0.38
Number of antibiotics before CAZ-AVI, median (IQR)	3 (2-3)	3 (3-6)	0.19	3 (2-3)	3 (3-6)	0.15	3 (2-4)	3 (2-4)	0.75
Life-threatening infection	15 (57.7%)	8 (66.7%)	0.73	14 (58.3%)	9 (64.3%)	1.00	12 (52.2%)	11 (73.3%)	0.31
Carbapenemase <sup>a</sup>									
KPC	17 (68.0%)	6 (54.6%)	0.48	18 (75.0%)	5 (41.7%)	0.07	17 (77.3%)	6 (42.9%)	0.07
OXA-48	8 (32.0%)	5 (45.5%)		6 (25.0%)	7 (58.3%)		5 (22.7%)	8 (57.1%)	
Polymicrobial infection	6 (23.1%)	5 (41.7%)	0.27	4 (16.7%)	7 (50.0%)	0.06	6 (26.1%)	5 (33.3%)	0.72
cIAI or CUTI as sole infection site (with or without bacteremia)	10 (38.5%)	3 (25.0%)	0.49	7 (29.2%)	6 (42.9%)	0.49	9 (39.1%)	4 (26.7%)	0.50
Bacteremia	18 (69.2%)	8 (66.7%)	1.00	18 (75.0%)	8 (57.1%)	0.30	15 (65.2%)	11 (73.3%)	0.73
Surgery to remove the source of infection before or during CAZ-AVI	13 (50.0%)	6 (50.0%)	1.00	11 (45.8%)	8 (57.1%)	0.74	12 (52.2%)	7 (46.7%)	1.00
Mechanical ventilation at start of CAZ-AVI	8 (30.8%)	6 (50.0%)	0.30	8 (33.3%)	6 (42.9%)	0.73	5 (21.7%)	9 (60.0%)	0.04
On vasopressors at start of CAZ-AVI	11 (42.3%)	6 (50.0%)	0.73	10 (41.7%)	7 (50.0%)	0.74	8 (34.8%)	9 (60.0%)	0.19
Unconscious at start of CAZ-AVI	6 (23.1%)	6 (50.0%)	0.14	6 (25.0%)	6 (42.9%)	0.30	4 (17.4%)	8 (53.3%)	0.03
Concurrent active antibiotic treatment <sup>b</sup>	18 (69.2%)	7 (58.3%)	0.71	16 (66.7%)	9 (64.3%)	1.00	14 (60.9%)	11 (73.3%)	0.50
Received standard CAZ-AVI dose	17 (65.4%)	7 (58.3%)	0.73	15 (62.5%)	9 (64.3%)	1.00	15 (65.2%)	9 (60.0%)	1.00

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<sup>a</sup> Among 36 patients with Enterobacteriaceae	519
<sup>b</sup> During CAZ-AVI treatment, patient received another antibiotic to which organism was non-resistant <i>in vitro</i>	520

