J Antimicrob Chemother 2021; **76**: 1025–1031
doi:10.1093/jac/dkaa549 Advance Access publication 30 December 2020

Journal of Antimicrobial Chemotherapy

Pragmatic options for dose optimization of ceftazidime/avibactam with aztreonam in complex patients

Marco Falcone [1]*, Francesco Menichetti[1], Dario Cattaneo[2], Giusy Tiseo[1], Sara Baldelli[2], Valentina Galfo[1], Alessandro Leonildi[1,3], Enrico Tagliaferri[1], Antonello Di Paolo[4] and Manjunath P. Pai [5]

[1]Infectious Diseases Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliera Universitaria Pisana, University of Pisa, Pisa, Italy; [2]Unit of Clinical Pharmacology, ASST Fatebenefratelli Sacco University Hospital, Milan, Italy; [3]Microbiology Unit, Azienda Ospedaliera Universitaria Pisana., Pisa, Italy; [4]Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [5]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI, USA

*Corresponding author. E-mail: marco.falcone@unipi.it

Received 10 September 2020; accepted 4 December 2020

Background: Avibactam is a β-lactamase inhibitor that is combined with aztreonam against Enterobacterales co-expressing serine- and metallo-β-lactamases (MBL). Optimal dosing of aztreonam with avibactam is not well-defined in critically ill patients and contingent on ceftazidime/avibactam product labelling.

Objectives: To identify a pragmatic dosing strategy for aztreonam with avibactam to maximize the probability of target attainment (PTA).

Methods: We conducted a prospective observational pharmacokinetic study. Five blood samples were collected around the fourth dose of aztreonam or ceftazidime/avibactam and assayed for all three drugs. Population pharmacokinetic (PK) analysis coupled with Monte Carlo simulations were used to create a dosing nomogram for aztreonam and ceftazidime/avibactam based on drug-specific pharmacodynamic (PD) targets.

Results: A total of 41 participants (59% male) median age of 75 years (IQR 63–79 years) were enrolled. They were critically ill (46%) with multiple comorbidities and complications including burns (20%). Population PK analysis identified higher volume of distribution and lower clearance (CL) compared with typical value expectations for aztreonam and ceftazidime/avibactam. Estimated glomerular filtration (eGFR) rate using the CKD-EPI equation predicted CL for all three drugs. The need for high doses of aztreonam and ceftazidime/avibactam above those in the existing product labels are not predicted by this analysis with the exception of ceftazidime/avibactam for patients with eGFR of 6–15 mL/min, in whom suboptimal PTA of $\leq$71% is predicted.

Conclusions: Pragmatic and lower daily-dose options are predicted for aztreonam and ceftazidime/avibactam when the eGFR is <90 mL/min. These options should be tested prospectively.

Introduction

Aztreonam is active against serious Gram-negative bacterial pathogens that express metallo-β-lactamases, against which other β-lactams are ineffective.[1] The activity of aztreonam is lost against bacterial strains that co-produce serine-β-lactamases; this activity can be restored by the β-lactamase inhibitor, avibactam.[1–4] Phase 3 trials testing the combination of aztreonam/avibactam are underway. In the interim, aztreonam is added to commercially available ceftazidime/avibactam to practicably deliver this combination. Our group recently performed a prospective observational study and demonstrated a 3-fold lower 30-day mortality with this ceftazidime/avibactam plus aztreonam regimen compared with existing antimicrobial combinations.[5]

While these results are promising, an important caveat is that current dosing of avibactam is based on the activity of this agent in combination with ceftazidime and remains to be optimized for its use with aztreonam. *In vitro* studies suggest that aztreonam doses of 8 g/day as a continuous or 2 h infusion in combination with 2.5 g every 8 h of ceftazidime/avibactam to be optimal for bacterial eradication and resistance suppression.[6] These *in vitro* studies provide critical information to define dosing regimens and rely on assumptions of population pharmacokinetics that may require optimization for specific populations that are underrepresented in clinical trials. These underrepresented populations include patients with burns, in septic shock, and those with organ dysfunction. Acute kidney injury is common among critically ill patients, which is relevant as kidney function is estimated and used to alter the

dosing of aztreonam and ceftazidime/avibactam. Therapeutic drug monitoring has a role for dose adaptation in this setting but is not readily available for widespread use. Therefore, our primary objective was to identify a pragmatic dosing strategy for this triple drug combination in order to maximize the PTA. In order to accomplish this goal, we interrogated patient demographics, body size, organ dysfunction, and health status factors as covariates to inform specific population dosing. We simulated multiple dosage regimens to identify potential combination treatments that optimized pharmacodynamic targets to identify interventions for future prospective studies.

Patients and methods

Study design and patient population

This prospective observational pharmacokinetic study included the recruitment of patients treated with ceftazidime/avibactam or the combination of ceftazidime/avibactam with aztreonam between July 2019 and February 2020. Patients were eligible for inclusion in the study if: (1) ≥18 years of age; (2) culture-positive for carbapenemase-producing Enterobacterales (CPE); and (3) planned receipt of ceftazidime/avibactam for at least 48 h. All patients were followed-up until 30 days after the infection episode or culture positivity.

Ethics

The study was conducted according to the principles stated in the Declaration of Helsinki. The Ethics Committee of the participating hospitals approved the study protocol (approval number 16761).

Microbiological studies

Blood isolate identification and the presence of the *bla* genes for carbapenemases (NDM, VIM, KPC or others) were verified as previously described.[5] MICs for aztreonam and ceftazidime/avibactam were performed on all isolates according to the breakpoints established by the European Committee on Antimicrobial Susceptibility Testing.[7] A checkerboard broth microdilution assay was used to assess the synergy of ceftazidime/avibactam with aztreonam and the fractional inhibitory concentration index (FICI) was calculated. Checkerboards were set up with 2-fold dilutions of aztreonam (0.03–128 mg/L) and ceftazidime/avibactam (1–0.25 to 64–16 mg/L, respectively) as previously described.[8]

Antibiotic dosing and sampling

Study participants received a regimen of ceftazidime/avibactam 2 g/0.5 g every 8 h as a 2 h intermittent infusion or as a continuous infusion. These regimens were either administered alone or in combination with aztreonam 2 g every 8 h as a 2 h infusion. Ceftazidime/avibactam and aztreonam were given simultaneously. The specific regimen selection was at the discretion of the prescribing physician. A blood sample was collected: prior to administration of the first dose; just prior to administration of the fourth dose; at the end of the infusion; around the midpoint of the dosing interval; and prior to the fifth dose. For continuous infusion regimens, similar sampling was performed with use of a 2 h timepoint substituting for the 'end of infusion' sample.

Sample analysis

Blood samples were centrifuged and plasma samples stored at −80°C until analysis. Ceftazidime, avibactam and aztreonam concentrations were determined using an ultraperformance liquid chromatography tandem mass spectrometry method, which was validated according to the European Medicines Agency (EMA) Guidelines. After purification through precipitation and dilution with a solution of methanol, acetonitrile and water 0.1% formic acid, 1 μL was injected. Chromatographic separation was achieved using a gradient (acetonitrile and water with formic acid 0.1%) on a reversed-phase analytical column (Acquity UPLC BEH C18 1.70 μm 2.1 × 50 mm; Waters, Milan, Italy). For quantification, analysis was performed in ESI-positive mode by monitoring the transition $m/z = 274.10 > 79.9$ for ceftazidime and the transition $m/z = 436.02 > 313.09$ for aztreonam; while for avibactam ESI-negative mode was applied with the transition 263.94 > 96.07. The limit of quantification was set at 0.4 mg/L for aztreonam and avibactam and 0.8 for ceftazidime.

Inaccuracy and imprecisions had values between 1.4% and 13.2%. According to EMA guidelines on Bioanalytical Method Validation the assay was considered acceptable if imprecision and inaccuracy at each concentration was <15% for both within- and between-day analysis. At the limit of quantification, inaccuracy and imprecision had to be <20%. The performance of the method was tested during each analytical run using internal quality controls with concentrations that cover the entire range of the calibration curve, and blinded samples, in case of ceftazidime, sent as part of the Instand Proficiency Testing Schemes for Antibiotic Drugs (detailed information are available at http://www.instand-ev.de/). An individual batch run was accepted if two-thirds of all QC samples had concentrations within 15% of the theoretical ones.

Data collection and management

Participant demographics, past medical history, laboratory, and health status scores were collected. Demographic information included age, sex, race, height and weight. The presence or absence of the following conditions were recorded, HIV, neutropenia, solid cancer, haematological malignancy, diabetes, solid organ transplant, chronic obstructive pulmonary disease, chronic liver disease, cardiovascular disease, chronic kidney disease, invasive mechanical ventilation, septic shock, burns, and need for continuous renal replacement therapy (CRRT). Health status scores included age-adjusted Charlson Comorbidity Index, Glasgow Coma Scale, Sequential Organ Failure Assessment, systolic and diastolic blood pressure as well as mean arterial pressure.[9] Laboratory measurements included lactate concentrations, white blood cell counts, platelet counts, serum creatinine, blood urea nitrogen, bilirubin, transaminases and albumin. Alternative body size scalars including ideal body weight (IBW), adjusted body weight (adjBW), and body surface area (BSA) using Mosteller's adaptation were computed as previously described.[10] We calculated estimated creatinine clearance (eCL_{CR}) using the Cockcroft–Gault equation with total body weight (TBW), IBW, adjBW, and a dosing weight (DW). The DW was based on the principle for use of IBW or TBW if TBW<IBW or adjBW if $TBW > 1.25 \times IBW$.[11] The estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.[12,13] Given that the product labels for these antibiotics rely on kidney function estimates in mL/min, we transformed eGFR into those units. All data management, organization, and exploratory analyses were performed on de-identified data in the R environment.[14]

Pharmacokinetic analysis

Given the large number of potential covariates collected for this analysis, a two-step approach was used for population pharmacokinetic (PK) analyses and model construction. The first stage included was performed using Pkanalix2019R2 (non-compartmental analysis), Monolix2019R2, and Sycomore2019R2 (Monolix Suite2019R2, Antony, France: Lixoft SAS, 2019). For population PK analysis, the stochastic approximation expectation maximization (SAEM) algorithm was used within Monolix2019R2 and individual aztreonam and ceftazidime/avibactam dosing and concentration–time data. We tested both 1- and 2-compartment, first order input and linear clearance parameterized model structures based on semi-logarithmic

concentration–time profiles. Initial parameter estimates were set to literature values, and in the case of ceftazidime/avibactam to those used to justify the current product label. An automatic covariate-building model using the stepwise covariate model (SCM) that includes both forward selection and backward elimination with discrimination at each iteration using Bayesian Information Criteria that also penalizes the population parameters from random and non-random individual parameter models as well as the number of subjects (BICc). After completion of this covariate selection, the second-step included parameter estimation using the non-parametric adaptive grid algorithm within the Pmetrics™ package for the R environment.[14–16] This approach was taken to ensure derivation of robust parameter estimates given the heterogeneity of the underlying population.

Monte Carlo simulation

Dosing regimens were assessed using 1000-subject Monte Carlo Simulations within Pmetrics™. The final model covariate matrix and model structure was used as the population distribution for the simulation runs. We simulated aztreonam doses of 1–2 g every 6 to 8 h, and up to 8 g/day by continuous infusion after a 2 g loading dose in virtual patients with an eGFR of 15–150 mL/min. PTA for aztreonam was $AUC_{0-24}/MIC \geq 184$, and $\%fT_{>MIC}$ of at least 50% for the 0–24 h period based on $\log_2$ MIC values of 1 to 32 mg/L.[16] Similar simulations (across eGFR) were performed with ceftazidime/avibactam doses (2 h infusion) of 1 g/0.25 g to 2 g/0.5 g every 6 to 12 h. The PTA for ceftazidime was based on $\%fT_{>MIC}$ of at least 50% for the 0–24 h period for MIC values of 1 to 32 mg/L.[17] The PTA for avibactam was based $\%fT_{>CT}$ of at least 50% for the zero to 24 h period based on concentration-threshold (CT) values of 1, 2, and 4 mg/L.[18] We also simulated virtual patients with 6–15 mL/min, 16–30 mL/min, 31–50 mL/min, and >50 mL/min as their kidney function estimate to match the ceftazidime/avibactam label. Plasma protein binding of 50%, 10%, and 5% were used for aztreonam, ceftazidime, and avibactam, respectively.[16–18]

Results

The study sample included 41 adults with BMI values of 16–35 kg/m^2. Patients characteristics are reported in Table 1. Patients were elderly with a median age of 75 years (IQR, 63–79 years) and 58.5% male. Most (90%) patients were not obese (BMI < 30 kg/m^2), with a body weight range of 45–95 kg and height range of 158–185 cm. Baseline median serum creatinine was 1.16 mg/dL (range, 0.24–4.22 mg/dL) and 1.08 mg/dL (range, 0.73–2.76 mg/dL) in patients without ($n = 35$) and with the need for CRRT ($n = 6$). Patients had multiple comorbidities including cancer (49%), diabetes (51%), cardiovascular disease (54%), chronic kidney disease (36%), and chronic obstructive pulmonary disease (12%). 46% of patients were cared for in the ICU, and 12 (29.3%) had septic shock. Eight patients (19.5%) had burn injuries. The most common sources of infection were urinary tract (29.3%), respiratory tract (24.4%), central venous catheter (22.0%), and skin and skin structure related (14.6%). At 30 days, a 27% rate of mortality was recorded in this study sample.

Thirty-five patients received the combination ceftazidime/avibactam plus aztreonam because of infection due to NDM-producing Enterobacterales, while 6 patients were treated with ceftazidime/avibactam alone for infections caused by KPC-producing strains. NDM-producing *K. pneumoniae* belonged to the same clonal lineage, sequence type (ST) 147. *K. pneumoniae* isolates carried the bla_{NDM-1} gene and a clonal analysis revealed that all the ST147 isolates were closely related to each other, suggesting that the outbreak was due to clonal expansion of a single NDM-1-producing *K. pneumoniae* strain.[2,19] All NDM strains of *K. pneumoniae* were resistant to aztreonam (MIC > 32 mg/L) and to ceftazidime/avibactam (MIC > 8/4 mg/L). The MIC of aztreonam at an avibactam concentration of 4 mg/L was 0.25 mg/L. Using checkerboard analyses, the fractional inhibitory concentration index (FICI) for ceftazidime/avibactam and aztreonam was 0.03.

The most common ceftazidime/avibactam dosage was 2 g/0.5 g (73%) every 8 h and was used in four of six patients on CRRT. With the exception of one patient treated with 1 g/0.25 g (eGFR of 11 mL/min), the remaining patients were treated with 1 g/0.25 g of ceftazidime/avibactam every 8 h. Similarly, aztreonam was dosed as 1 or 2 g every 8 h with the exception of 1 g every 24 h in one patient. The median (range) C_{min} of aztreonam, ceftazidime, avibactam after the fifth dose was 53.6 (1.5–176), 57.9 (1.2–175), and 10.9 (0.4–46.3) mg/L, respectively. Treatment prior to sample

Table 1. Baseline demographic and clinical characteristics of patients

Characteristics	Patients ($N = 41$)
Demographics	
Age, years, median (IQR)	75 (63–79)
Male sex, *n* (%)	24 (58.5)
BMI, kg/m^2, median (IQR)	23.9 (231.5–26)
BMI >30 kg/m^2, *n* (%)	3 (7.3)
Ward of hospitalization, *n* (%)	
Medical ward	16 (39)
Surgery	5 (12.5)
ICU	20 (48.8)
Comorbidities, *n* (%)	
Cardiovascular disease	22 (53.7)
Diabetes mellitus	21 (51.2)
Cancer	20 (48.8)
CKD	15 (36.6)
COPD	5 (12.2)
Chronic liver disease	4 (9.7)
Solid organ transplantation	2 (4.9)
Burns	8 (19.5)
Baseline laboratory parameters	
Creatinine values, mg/dL, median (IQR)	1.14 (0.64–1.92)
BUN, mg/dL, median (IQR)	30 (15–43)
Albumin values, g/dL, median (IQR)	2.7 (2.3–2.9)
Bilirubin, g/dL, median (IQR)	0.53 (0.38–0.84)
Septic shock, *n* (%)	12 (29.3)
Bacteraemia, *n* (%)	26 (63.4)
Source of infection, *n* (%)	
Urinary-tract infection	12 (29.3)
Respiratory tract infection	10 (24.4)
CVC-related bacteraemia	9 (22)
Skin and skin structure infection	6 (14.6)
Intra-abdominal infection	4 (9.8)
Aetiology, *n* (%)	
NDM-producing Enterobacterales	35 (85.4)
KPC-producing Enterobacterales	6 (14.6)
30 day mortality, *n* (%)	11 (26.8)

BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase.

Table 2. Population pharmacokinetic parameter estimates reported as the median (percentage interindividual variability)

Model	Aztreonam	Ceftazidime	Avibactam
Base model			
V_d (L)	45.9 (52.9%)	26.3 (114%)	40.2 (98.7%)
CL (L/h)	3.3 (82.6%)	3.2 (82.0%)	4.9 (76.4%)
Final model			
V_d	32.0 (61.0%)	28.5 (67.0%)	41.6 (88.5%)
θ_1	1.8 (62.4%)	2.5 (39.0%)	3.5 (45.7%)
θ_2	0.9 (91.2%)	NA	0.7 (113%)
β	1.2 (37.7%)	1.2 (25.0%)	1.3 (34.7%)

NA, not available; V_d, volume of distribution; CL, clearance; Drug CL = $\theta_1 \times (\text{CKD-EPI}/50)^{\beta} + \theta_2$, where CKD-EPI is the chronic kidney disease epidemiology equation estimated glomerular filtration rate (in mL/min) transformed with body surface area.

analysis was a combination of ceftazidime/avibactam and aztreonam (85.4%) or ceftazidime/avibactam alone (14.6%).

A 1-compartment model with an additive and proportional error model provided a better fit to the data than 2-compartment models and alternate error model structure. Variables such as weight, comorbidities, septic shock, burns, or use of CRRT were not retained as covariates of aztreonam, ceftazidime or avibactam PK parameters once estimated kidney function was factored. Specifically, the CKD-EPI equation with eGFR in mL/min had the lowest Akaike information criterion (AIC) of all the models tested. This model was automatically selected for all three agents by SCM algorithm. The parameter estimates of the base and final covariate structured model using the NPAG are included in Table 2 for all three agents.

Figure 1 illustrates the probability of target attainment for aztreonam by dose and eGFR category. As shown, dosing aztreonam based on the current label is expected to achieve ≥90% PTA when the eGFR is <90 mL/min when based on $T_{>MIC}$ pharmacodynamic (PD) index and when the MIC is ≤4 mg/L. Table 3 includes the dosage regimens predicted to achieve ≥90% PTA based on the PD index, eGFR, and MIC. Use of $\%fT_{>MIC}$ predicts the need for lower doses with the potential for conventional dosing approaches for aztreonam MIC values ≤4 mg/L. Reliance on the AUC/MIC PD target was far more stringent than $\%fT_{>MIC}$ for aztreonam and suggested an MIC values ≤1 mg/L to be appropriate for conventional dose selection. Table 3 also includes the PTA for ceftazidime/avibactam by MIC and eGFR group. Lower than conventional doses are predicted for ceftazidime/avibactam based on the current MIC/concentration-threshold of 4/1 mg/L for this agent. The labelled dose of ceftazidime/avibactam is 0.94 g/0.19 g every 12 h and 24 h when the kidney function is 16–30 mL/min and 6–15 mL/min with a predicted PTA of 61% and 71%, respectively, at the aforementioned threshold.

Discussion

Limited therapeutic options exist to manage patients with serious infections due to Gram-negative bacilli that express MBL.[10,20,21] Recent *in vitro* studies indicate that aztreonam doses of 2 g every 6 h or 8 g per day by continuous infusion are necessary when combined with ceftazidime/avibactam 2 g/0.5 g every 8 h to treat these infections.[6] These *in vitro* findings are expected to yield conservative dosing strategies, as they cannot fully recapitulate the complex physiological and immunological processes in patients with these infections. Our study was designed to better inform potential clinical dosing strategies by bridging PK information gained from this clinical study with *in vitro* PD studies. Our findings yield a more nuanced consideration for dosage selection in this population and predict lower doses for patients with renal impairment.

The patients included in this analysis had multiple comorbidities and complications, which is reflected by high interindividual variability in PK parameters. Typical variables such weight, age, and conditions such as burns, use of CRRT, and septic shock were supplanted by estimated kidney function as the primary covariate influencing aztreonam and ceftazidime/avibactam PK. Similar convergence of covariates to eGFR based on the CKD-EPI equations has recently been demonstrated with imipenem.[22] The high Vd (30–50 L) for these agents noted in our population relative to healthy participants (5–10 L) is consistent with findings seen with aztreonam and ceftazidime/avibactam in critically ill patients.[11,23] Our results align well with previous PopPK analyses of ceftazidime/avibactam.[24,25] However, the observed average aztreonam CL was 6.4 L/h (median 51 years) in a recent study of patients with complicated intra-abdominal infections compared with 3.3 L/h (median 75 years) in our study.[26] The CL of aztreonam and ceftazidime/avibactam observed in our population was approximately 50% lower than previous studies.[16,26] Prior studies have shown strong correlations between CL for all three agents and kidney function.[14–16] Lower drug CL in our population is explained by studying an elderly population with a mean eGFR of 50 mL/min, and the presence of chronic kidney disease (CKD) in a third of our population. The population model used to justify the ceftazidime/avibactam label also incorporated a 20% reduction in avibactam CL in critically ill patients with an APACHE II score >10 compared with non-critically ill patients.[20] Lower CL of avibactam in critically ill patients implies that higher doses are less likely to be needed in this population, and the low protein binding (5%) for the compound also marginalizes the contribution of this variable.

Our modelling and simulations revealed that the currently approved dosing strategies for aztreonam and ceftazidime/avibactam meet the time-dependent PD targets for these agents. If an isolate between the current susceptible and resistant criteria is observed (aztreonam MIC = 8 mg/L), use of 2 g every 6 h may be optimal when the eGFR is 90–120 mL/min and may require one 2 g IV dose followed by 8 g/day as continuous infusion when the eGFR is >120 mL/min. However, these regimens are less likely because the combination of aztreonam with avibactam lowered the MIC of aztreonam to ∼0.25 mg/L. Our PD target attainment was based on 50% $fT_{>MIC}$ and so our projections at an aztreonam MIC of 4–8 mg/L (Table 3) are 16–32-fold above this expectation (i.e. very conservative). Likewise, the use of ceftazidime/avibactam at regulatory approved doses exceeds the threshold in all instances except at the recommended doses when eGFR is 6–15 mL/min. The current recommendation of every 24 h may need reappraisal to every 12 h to achieve the PD target. An alternative strategy for ceftazidime/avibactam at 1 g/0.25 g every 6 h was identified when combined with aztreonam, allowing for a reduction in the total daily dose compared with the conventional 2 g/0.5 g every 8 h regimen.

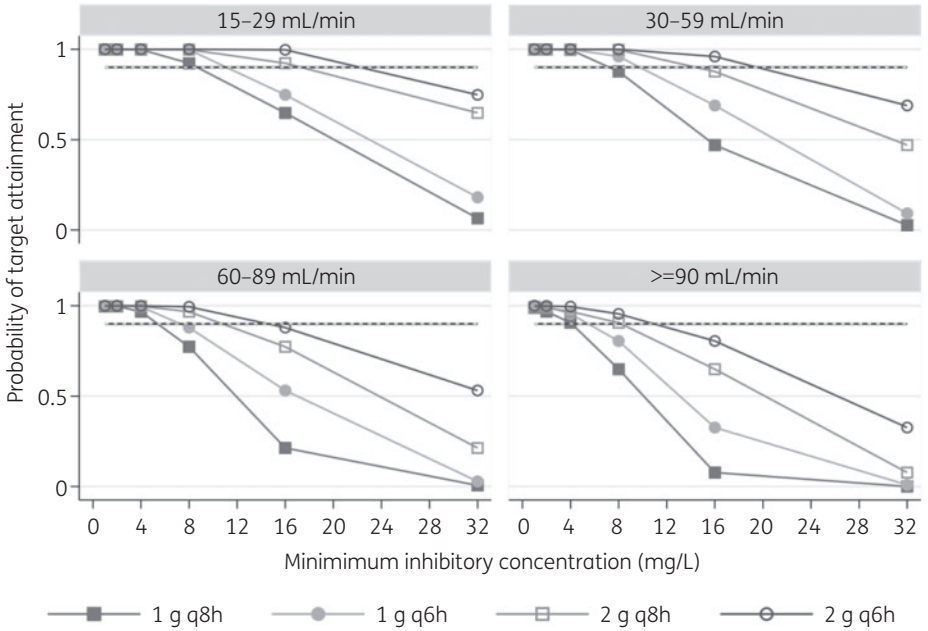

Figure 1. Probability of achieving $\%fT_{>MIC}$ with alternate aztreonam doses as a 2 h infusion by estimated glomerular filtration rate categories.

Table 3. Lowest simulated dose predicted to achieve ≥90% PTA by estimated glomerular filtration rate (eGFR) group as a 2 h infusion

	MIC (mg/L)[a] or concentration threshold (for avibactam)					
eGFR (mL/min)	1	2	4	8	16	32
Aztreonam						
15–30	1 g q8h	1 g q8h	1 g q8h	1 g q8h	1 g q8h	X
30–60	1 g q8h	1 g q8h	1 g q8h	1 g q8h	2 g q6h	X
60–90	1 g q8h	1 g q8h	1 g q8h	2 g q8h	2 g × 1, 8 g CI[b]	X
90–120	1 g q8h	1 g q8h	1 g q8h	2 g q6h	X	X
>120	1 g q8h	1 g q8h	1 g q6h	2 g × 1, 8 g CI[b]	X	X
Ceftazidime						
15–30	1 g q12h	1 g q12h	1 g q12h	1 g q12h	1 g q12h	X
30–60	1 g q12h	1 g q12h	1 g q12h	1 g q12h	1 g q6h	X
60–90	1 g q12h	1 g q8h	1 g q12h	1 g q8h	2 g q8h	X
90–120	1 g q12h	1 g q8h	1 g q8h	1 g q6h	X	X
>120	1 g q12h	1 g q8h	1 g q6h	2 g q8h	X	X
Avibactam						
15–30	0.25 g q12h	0.25 g q12h	0.25 g q6h	X	X	X
30–60	0.25 g q12h	0.25 g q8h	0.25 g q6h	X	X	X
60–90	0.25 g q8h	0.25 g q6h	0.25 g q6h	X	X	X
90–120	0.25 g q8h	0.25 g q6h	0.5 g q8h	X	X	X
>120	0.25 g q6h	0.25 g q6h	X	X	X	X

X indicates that target attainment was not achievable by the tested regimen.
[a]The MICs for aztreonam and ceftazidime are based on the presence of avibactam.
[b]Denotes a 2 g dose over 2 h followed by continuous infusion (CI) of 8 g over the remaining 22 h for the 24 h target attainment period.

Our study has many limitations linked in large part to the small sample size from an elderly population. We were not able to identify alternative covariates in part due to sample size. Although this was not our intention, a correlation of PK/PD with clinical outcomes is not reliable with this sample size. In defence of our work, the study samples were collected prospectively and analysed per protocol in a difficult to recruit and often under-represented study population. Also, large population PK studies have only identified estimated kidney function to be an actionable method for dose modification. In the case of aztreonam and ceftazidime/

avibactam this dose adjustment is based on estimated creatinine clearance using the Cockcroft–Gault formula. We show that the CKD-EPI equation is more reliable and practical given that institutions report eGFR in their electronic medical record using this formula. As with any observational study, our findings require future validation but provide hope when facing challenges such as limited drug supplies or need to lower costs in economically disadvantaged countries where MBL-producing Enterobacterales may be endemic.

In conclusion, we found that the approved dosing strategies for ceftazidime/avibactam and aztreonam meet PD targets when the estimated glomerular filtration rate is <90 mL/min in a complex population of critically ill patients with multiple comorbidities. These findings are likely to be driven by markedly lower CL in this elderly population cohort than in previous studies, and so should be confirmed by further studies in the critically ill.

Funding

This study was supported by internal funding (University of Pisa and Azienda Ospedaliera Universitaria Pisana).

Transparency declarations

The authors declare the following conflict of interests: M.F. received speaker honoraria from Angelini, MSD, Shionogi and Nordic Pharma. F.M. has participated in advisory boards and/or received speaker honoraria from Angelini, Correvio, MSD, Pfizer, Astellas, Gilead, BMS, Janssen, ViiV, BioMérieux, Biotest, Becton-Dickinson, Nordic Pharma, Pfizer and Shionogi. D.C. received consultant's fee from Viiv healthcare, and speaker honoraria from MSD, Janssen and Viiv. M.P.P. reports personal fees from Paratek Pharmaceuticals, personal fees from Wolters Kluwer, grants from Merck & Company, outside the submitted work. All conflicts of interest declared are outside the submitted study. The remaining authors have none to declare.

References

1 Emeraud C, Escaut L, Boucly A *et al*. Aztreonam plus clavulanate, tazobactam, or avibactam for treatment of infections caused by metallo-β-lactamase-producing Gram-negative bacteria. *Antimicrob Agents Chemother* 2019; **63**: pii:e00010–19.

2 Falcone M, Tiseo G, Antonelli A *et al*. Clinical features and outcomes of bloodstream infections caused by New Delhi Metallo-β-Lactamase-producing *Enterobacterales* during a regional outbreak. *Open Forum Infect Dis* 2020; **7**: ofaa011.

3 Biagi M, Wu T, Lee M *et al*. Searching for the optimal treatment for metallo- and serine-β-lactamase producing Enterobacteriaceae: aztreonam in combination with ceftazidime-avibactam or meropenem-vaborbactam. *Antimicrob Agents Chemother* 2019; **63**: e01426–19.

4 Falcone M, Viale P, Tiseo G *et al*. Pharmacokinetic drug evaluation of avibactam + ceftazidime for the treatment of hospital-acquired pneumonia. *Expert Opin Drug Metab Toxicol* 2018; **14**: 331–40.

5 Falcone M, Daikos GL, Tiseo G *et al*. Efficacy of ceftazidime-avibactam plus aztreonam in patients with bloodstream infections caused by MBL- producing *Enterobacterales*. *Clin Infect Dis* 2020; ciaa586.

6 Lodise TP, Smith NM, O'Donnell N *et al*. Determining the optimal dosing of a novel combination regimen of ceftazidime/avibactam with aztreonam against NDM-1-producing Enterobacteriaceae using a hollow-fibre infection model. *J Antimicrob Chemother* 2020; **75**: 2622–32.

7 European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0. 2020. http://www.eucast.org.

8 Yasmin M, Fouts DE, Jacobs MR *et al*. Monitoring ceftazidime-avibactam (CAZAVI) and aztreonam (ATM) concentrations in the treatment of a bloodstream infection caused by a multidrug-resistant *Enterobacter* sp carrying both KPC-4 and NDM-1 carbapenemase. *Clin Infect Dis* 2020; **71**: 1095–8.

9 Falcone M, Bassetti M, Tiseo G *et al*. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing *Klebsiella pneumoniae*. *Crit Care* 2020; **24**: 29.

10 Pai MP. Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. *Pharmacotherapy* 2012; **32**: 856–8.

11 Traynor AM, Nafziger AN, Bertino JS Jr. Aminoglycoside dosing weight correction factors for patients of various body sizes. *Antimicrob Agents Chemother* 1995; **39**: 545–8.

12 Levey AS, Coresh J, Greene T *et al*. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–54.

13 Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate [published correction appears in Ann Intern Med. 2011 Sep 20;155(6):408]. *Ann Intern Med* 2009; **150**: 604–12.

14 R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. 2020. https://www.R-project.org/.

15 Neely MN, van Guilder MG, Yamada WM *et al*. Accurate detection of outliers and subpopulations with pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. *Ther Drug Monit* 2012; **34**: 467–76.

16 Xu H, Zhou W, Zhou D *et al*. Evaluation of aztreonam dosing regimens in patients with normal and impaired renal function: a population pharmacokinetic modeling and Monte Carlo simulation analysis. *J Clin Pharmacol* 2017; **57**: 336–44.

17 Li J, Lovern M, Green ML *et al*. Ceftazidime-avibactam population pharmacokinetic modeling and pharmacodynamic target attainment across adult indications and patient subgroups. *Clin Transl Sci* 2019; **12**: 151–63.

18 Nichols WW, Newell P, Critchley IA *et al*. Avibactam pharmacokinetic/pharmacodynamic targets. *Antimicrob Agents Chemother* 2018; **62**: e02446-17.

19 Tavoschi L, Forni S, Porretta A *et al*. Prolonged outbreak of New Delhi metallo-β-lactamase-producing carbapenem-resistant *Enterobacterales* (NDM-CRE), Tuscany, Italy, 2018 to 2019. *Euro Surveill* 2020; **25**: pii=2000085.

20 Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR Gram-negative infections. *J Antimicrob Chemother* 2016; **71**: 2713–22.

21 Falcone M, Mezzatesta ML, Perilli M *et al*. Infections with VIM-1 metallo-β-lactamase-producing *Enterobacter cloacae* and their correlation with clinical outcome. *J Clin Microbiol* 2009; **47**: 3514–9.

22 de Velde F, de Winter BCM, Neely MN *et al*. Population pharmacokinetics of imipenem in critically ill patients: a parametric and nonparametric model converge on CKD-EPI estimated glomerular filtration rate as an impactful covariate. *Clin Pharmacokinet* 2020; **59**: 885–98.

23 Stein GE, Smith CL, Scharmen A *et al*. Pharmacokinetic and pharmacodynamic analysis of ceftazidime/avibactam in critically ill patients. *Surg Infect (Larchmt)* 2018; **20**: 55–61.

24 Das S, Li J, Riccobene T *et al.* dose selection and validation for ceftazidime-avibactam in adults with complicated intra-abdominal infections, complicated urinary tract infections, and nosocomial pneumonia. *Antimicrob Agents Chemother* 2019; **63**: e02187-18.

25 Sy SKB, Zhuang L, Sy S *et al.* clinical pharmacokinetics and pharmacodynamics of ceftazidime-avibactam combination: a model-informed strategy for its clinical development. *Clin Pharmacokinet* 2019; **58**: 545–64.

26 Cornely OA, Cisneros JM, Torre-Cisneros J *et al.* Pharmacokinetics and safety of aztreonam/avibactam for the treatment of complicated intra-abdominal infections in hospitalized adults: results from the REJUVENATE study. *J Antimicrob Chemother* 2020; **75**: 618–27.