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MINIREVIEW

Avibactam Pharmacokinetic/Pharmacodynamic Targets

Wright W. Nichols,[a] Paul Newell,[b]* Ian A. Critchley,[c]* Todd Riccobene,[d] Shampa Das[b]*

[a]AstraZeneca, Waltham, Massachusetts, USA
[b]AstraZeneca, Alderley Park, Macclesfield, United Kingdom
[c]Allergan plc, Irvine, California, USA
[d]Allergan plc, Madison, New Jersey, USA

ABSTRACT Avibactam is a novel non-β-lactam β-lactamase inhibitor that has been approved in the United States and Europe for use in combination with ceftazidime. Combinations of avibactam with aztreonam or ceftaroline fosamil have also been clinically evaluated. Until recently, there has been very little precedence of which pharmacokinetic/pharmacodynamic (PK/PD) indices and magnitudes are appropriate to use for β-lactamase inhibitors in population PK modeling for analyzing potential doses and susceptibility breakpoints. For avibactam, several preclinical studies using different *in vitro* and *in vivo* models have been conducted to identify the PK/PD index of avibactam and the magnitude of exposure necessary for effect in combination with ceftazidime, aztreonam, or ceftaroline fosamil. The PD driver of avibactam critical for restoring the activity of all three partner β-lactams was found to be time dependent rather than concentration dependent and was defined as the time that the concentration of avibactam exceeded a critical concentration threshold (%fT$>$C$_T$). The magnitude of the C$_T$ and the time that this threshold needed to be exceeded to elicit particular PD endpoints varied depending on the model and the partner β-lactam. This review describes the preclinical studies used to determine the avibactam PK/PD target in combination with its β-lactam partners.

KEYWORDS avibactam, diazabicyclooctane, BL-BLI, PK/PD

Selecting the dose of a candidate antibiotic for evaluation in clinical trials requires the translation of pharmacokinetic/pharmacodynamic (PK/PD) data derived from *in vitro* and *in vivo* experimental models to the prediction of clinical responses in patients (1–3). Data from preclinical studies are typically used to identify the PK/PD index that best describes the relationship between exposure and the antimicrobial effect for the antibiotic in question. The magnitude of this PK/PD index which produces the desired effect is termed the PK/PD target. Due to interindividual variation in human PKs, a population-based modeling approach is necessary to predict whether potential dosing regimens will result in the achievement of the PK/PD target in a substantial majority of patients (4, 5). Population PK models developed from patient PK data are used to simulate antibiotic exposures in a representative patient population and to predict the proportion of patients who would achieve a level of drug exposure that meets the prespecified PK/PD target, known as the "probability of target attainment" (PTA). Such analyses can thus guide the selection of a dosage regimen that is likely to result in a high PTA (>90%). Neglecting key considerations of these principles can lead to failures of clinical trials due to inadequate drug exposures needed to be effective against key target pathogens (6). This exposes patients to unnecessary risks and delays or prevents the availability of a drug that may address an unmet need. Thus, appropriately characterizing the PK/PD index and magnitude preclinically is a key step in dose selection.

Avibactam is a novel diazabicyclooctane non-β-lactam β-lactamase inhibitor which is active against Ambler class A, class C, and some class D β-lactamases (7). When

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Address correspondence to Wright W. Nichols, wrightnichols1@gmail.com.

* Present address: Paul Newell, F2G Ltd., Manchester, United Kingdom; Ian A. Critchley, Spero Therapeutics, Cambridge, Massachusetts, USA; Shampa Das, University of Liverpool, Liverpool, United Kingdom.

combined with ceftazidime, an antipseudomonal cephalosporin, avibactam restores the activity of ceftazidime against most multidrug-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*, including those producing extended-spectrum β-lactamases (ESBLs) and non-metallo-β-lactamase (non-MBL) carbapenemases (8–10). Ceftazidime-avibactam is approved in the United States for the treatment of adults with complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI), hospital-acquired bacterial pneumonia, and ventilator-associated bacterial pneumonia and in Europe for the treatment of adults with cIAI, cUTI, and hospital-acquired pneumonia (including ventilator-associated pneumonia) and patients with aerobic Gram-negative infections and limited treatment options (11, 12).

Avibactam has also been evaluated in combination with the β-lactams aztreonam and ceftaroline fosamil. Aztreonam is a monocyclic β-lactam (monobactam) that is stable in the presence of MBLs, but is hydrolyzed by ESBLs. In combination with avibactam, aztreonam is active *in vitro* and *in vivo* against *Enterobacteriaceae* that harbor an MBL with or without one or more class A or C or some class D serine β-lactamases (13–15). Ceftaroline fosamil, the prodrug of the active component ceftaroline, is a broad-spectrum cephalosporin with *in vitro* activity against Gram-positive bacteria and some non-ESBL-producing Gram-negative species; when combined with avibactam, ceftaroline has shown *in vitro* activity against *Enterobacteriaceae* producing various ESBLs (16). A phase 2 trial of aztreonam-avibactam in patients with cIAI is currently ongoing (NCT02655419); ceftaroline fosamil-avibactam has been evaluated in a phase 2 clinical trial in patients with cUTI (NCT01281462) (17, 18).

For β-lactam–β-lactamase inhibitor combinations, it is important to establish a PK/PD index for both components, i.e., the β-lactamase inhibitor as well as the β-lactam antibiotic (19). Until recently, there has been very little precedence for the PK/PD indices and magnitudes that are appropriate to use for β-lactamase inhibitors in population PK modeling for analyzing potential doses and susceptibility breakpoints for β-lactam–β-lactamase inhibitor combinations. A thorough characterization of the PD of β-lactamase inhibitors in combination with their partner antibiotics enables an optimization of the dosing regimen. This review describes the preclinical studies used to identify the PK/PD index of avibactam and the magnitudes of exposure necessary for effect in combination with the different β-lactams, ceftazidime, aztreonam, and ceftaroline fosamil.

PK/PD TARGETS IN ANTIBIOTIC DRUG DEVELOPMENT AND THE PRINCIPLE OF ESTABLISHING A PK/PD INDEX FOR A β-LACTAMASE INHIBITOR

Although PK/PD indices and magnitudes for antibiotics could theoretically be identified from clinical trials, it is not ethical to give doses which are so low that a proportion of patients are likely to fail therapy. If the agent is effective and the dose regimen is well designed, there are likely to be few exposure-related failures. In addition, patients with infections due to multidrug-resistant pathogens are often critically ill, and clinical outcomes may be confounded by underlying diseases and/or surgical interventions. Consequently, exposure-effect analyses from clinical trial data do not usually enable discriminatory PK/PD indices and magnitudes to be identified (6, 19). Exposure targets must therefore be derived, initially, from nonhuman experiments that measure antibacterial activity in terms of bacterial killing or from outcome measures such as morbidity or mortality in animal infection models. Fortunately, in the analysis of PK/PD targets of antibacterial agents, substantial understanding can be achieved from preclinical *in vitro* and *in vivo* laboratory studies and subsequent modeling (6, 20, 21). Antibacterial drug exposures that result in bacteriostasis or 10- to 100-fold bacterial killing in experimental models are broadly correlated with clinical efficacy (6, 22, 23).

The analysis of PK/PD targets for antibacterial agents differs in a key aspect from that for drugs directed at mammalian biology, in that the target is the infecting pathogen. The PK/PD target established preclinically in either *in vitro* or *in vivo* systems is therefore relevant in humans, although penetration into the infection site may need to be taken into consideration. The exposure (PK) component of the PK/PD relationships for

antibacterial agents is generally related to one of the following parameters, based on plasma concentrations of the unbound drug: C_{max} (the maximum plasma concentration of the drug during the dosing interval), AUC (the area under the plasma concentration-time curve, mostly considered over 24 h [AUC_{0-24}]), or $T>C_{crit}$ (time above a critical concentration of the drug as a proportion of the regular dosing interval [interdose period]). In addition, the variability in the susceptibility of target pathogens to the antibiotic also needs to be considered in the PK/PD target for dose finding (24, 25). For antibacterial agents, the respective PK/PD indices have been established as the ratios fC_{max}/MIC, *f*AUC/MIC, or *f*T>MIC, where the *f* symbol indicates that the concentration is that of "free" (unbound) drug (26, 27). The critical MIC used in setting PK/PD targets should be based on analyses of MIC distributions observed in global surveillance studies of contemporary isolates of key pathogens from the intended indications.

Certain classes of antibiotics tend to share PK/PD indices. In concordance with those for other β-lactam antibiotics, the PK/PD indices for ceftazidime, ceftaroline fosamil, and aztreonam are well established as *f*T>MIC. The initial hypothesis of the PD of avibactam in combination with β-lactams was based on the theoretical concept that if the avibactam exposure is effective, then the PD of the combination should be the same as that of the partner β-lactam (28), i.e., related to *f*T>MIC of the combination. Avibactam alone does not have significant antibacterial activity and thus does not change the PD of the β-lactam partner. For avibactam, different experimental approaches have been used to characterize the PD index of exposure best related to restoring the activity of the partner β-lactam under dynamic conditions, including in *in vitro* hollow-fiber models and *in vivo* mouse thigh and lung infection models, as described in the following sections.

AVIBACTAM PK/PD TARGETS IN COMBINATION WITH CEFTAZIDIME

Ceftazidime PK/PD target. The achievement of 50% *f*T>MIC for ceftazidime has been shown to be associated with the killing of *Enterobacteriaceae* and *P. aeruginosa* by ceftazidime in neutropenic mouse infection models (29–31) and with microbiological eradication in patients with Gram-negative infections (23, 32). These PK/PD correlates led to the use of 50% *f*T>MIC as the pivotal exposure for associating particular ceftazidime doses with PK/PD target attainment and in establishing interpretive MIC criteria (25, 33–35). A ceftazidime-avibactam MIC value of 8 mg/liter was chosen for the PK/PD target because global surveillance data had reported ceftazidime-avibactam MIC_{90} values of 0.5 to 1 mg/liter and ≤8 mg/liter for phenotypically and genotypically unselected clinical isolates of *Enterobacteriaceae* and *P. aeruginosa*, respectively (36–42).

Determination of the avibactam PK/PD target when combined with ceftazidime against *Enterobacteriaceae*. Taking the concept that with complete β-lactamase inhibition, the PK/PD profile of ceftazidime-avibactam would revert to the PK/PD profile of ceftazidime, it was important to identify the concentration of avibactam that must be maintained to achieve sufficient β-lactamase inhibition to protect the activity of ceftazidime. Thus, a "critical" or "threshold" concentration of avibactam (C_T) was defined as that which occurs during the exponential decline of the concentration of avibactam during a dose cycle, below which the inhibition of β-lactamases is inadequate to prevent growth (of ceftazidime-resistant bacteria) in the presence of ceftazidime.

A series of hollow-fiber model experiments were used to analyze the PK/PD activity of avibactam in restoring the bactericidal activity of ceftazidime against ceftazidime-resistant *Enterobacteriaceae* and thus determine the C_T of avibactam in this setting (43). In the first set of experiments, avibactam concentrations were varied to simulate human PK profiles, while ceftazidime was held constant at a concentration higher than that of the MIC of ceftazidime-avibactam in combination but lower than that of the MIC of ceftazidime alone for all strains tested. The three ceftazidime-resistant *Enterobacteriaceae* isolates used in these experiments produced either derepressed AmpC (*Enterobacter cloacae*) or one of two ESBLs, SHV-5 or CTX-M-15 (*Klebsiella pneumoniae*). The avibactam concentration below which adequate inhibition of β-lactamases was lost

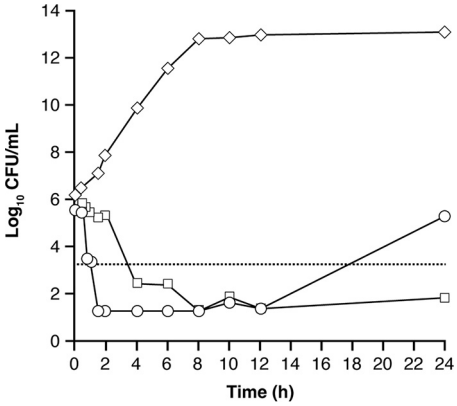

FIG 1 Responses of ceftazidime-resistant *E. cloacae* to continuous infusion of ceftazidime combined with two different concentration-time profiles of avibactam in the hollow-fiber model. Results are shown for isolate *E. cloacae* 293HT96 (stably derepressed AmpC; MIC ceftazidime, >128 mg/liter; MIC ceftazidime-avibactam, 4 mg/liter [with avibactam fixed at 4 mg/liter {59}]). ◇, untreated growth control; □, continuous infusion of ceftazidime (8.2 mg/liter) and avibactam (1.6 mg/liter); ○, continuous infusion of ceftazidime (8.2 mg/liter) with a single-dose profile of avibactam (C_{max}, 31 mg/liter at 0.5 h). The dotted line represents 99.9% bacterial killing. For the single-dose profile of avibactam, growth recommenced after the 12-h time point when the concentration of avibactam on the exponentially declining concentration-time curve was 0.15 mg/liter, resulting in an estimated critical concentration threshold (C_T) of ≤0.15 mg/liter. Adapted and republished from reference 43.

was identified as that at which bacterial numbers started to increase again. The magnitude of the C_T was estimated as being equal to or less than the concentration of avibactam remaining in the hollow-fiber system at the time point at which growth suppression was last experimentally demonstrated.

Figure 1 shows how C_T was estimated in these hollow-fiber experiments, using the *E. cloacae* isolate as an example. Four estimates of the C_T of avibactam were obtained with the three isolates, with a mean value of ≤0.21 mg/liter (range, ≤0.15 to ≤0.28 mg/liter). Several further observations about the C_T of avibactam were noteworthy from these experiments. The four values of C_T were similar, with similar C_T values obtained for two species: ≤0.15 and ≤0.2 mg/liter for *E. cloacae* and ≤0.22 and ≤0.28 mg/liter for *K. pneumoniae*. There was no direct correlation between the MIC of ceftazidime-avibactam (which spanned a 4-fold range of MICs studied [1 to 4 mg/liter] among the three isolates) and the C_T for each isolate and no obvious dependence on the specific β-lactamase encountered. Within these experiments, while the avibactam AUC_{0-24} ranged between 16.4 and 126 mg · h/liter, there was no relationship between growth suppression and the AUC (43).

In a second set of hollow-fiber experiments, the "growth suppression windows" yielded by constant concentrations of avibactam infused for different periods of time were determined using a broader panel of isolates (including *K. pneumoniae* carbapenemase [KPC]-3-producing *K. pneumoniae* and stably derepressed AmpC-producing *Citrobacter freundii*). In these experiments, constant concentrations of avibactam ranging from 0.25 to 1.0 mg/liter were infused for different time periods in the background of ceftazidime concentrations varied to simulate human PK profiles. This enabled a C_T of avibactam to be determined on the basis of a period of infusion of a constant concentration of the compound rather than following a peak of avibactam as described in the previous set of experiments. This was termed C_T^{Q8} to indicate that it was determined in a background of 8 hourly (q8h) cycling of ceftazidime concentrations. The C_T^{Q8} yielded in the background of ceftazidime exposures equivalent to a dose of 2 g q8h was ≤0.5 mg/liter. When comparing this value of C_T^{Q8} to the C_T to be used in setting a PK/PD target, it should be regarded a relatively conservative magnitude. This is because the avibactam concentration was constant and did not account for the pharmacologic effect of the higher avibactam concentrations yielded *in vivo* at early time points after dosing.

TABLE 1 Assessment of the hypothesis that $fT>C_T$ is the exposure variable more closely linked than *f*AUC to the pharmacodynamic effect of avibactam in combination with ceftazidime against ceftazidime-resistant *P. aeruginosa* in the neutropenic mouse lung infection model, using bacterial stasis as the pharmacodynamic endpoint[a]

			AVI[c]			
	MIC (mg/liter)		Static total daily dose (mg · kg^{-1} · day^{-1})		%*f*T>C_T of 1 mg/liter associated with stasis[d]	
Strain[b]	CAZ[e]	CAZ-AVI	q2h	q8h	q2h	q8h
11	128	16	45.6	463	19.7	20.9
18	32	2	56.4	151	23.5	16.1

[a]Constructed from the data of Berkhout et al. (44).
[b]Resistance summaries for the strains used in this experiment are as follows. Strain 11: OprD$^-$, AmpC^{con}, class A$^-$, class B$^-$; strain 18: OprD$^-$, AmpC$_{ind}$?, class A$^-$, class B$^-$.
[c]AVI, avibactam.
[d]Stasis-associated exposure times as percentages of the dosing interval calculated to be yielded by the interpolated doses shown.
[e]CAZ, ceftazidime.

Taking together the results from these hollow-fiber experiments, a minimum avibactam C_T of 0.5 mg/liter was considered appropriate for estimating the PTA for ceftazidime-avibactam against *Enterobacteriaceae* (43). As there was no relationship between the C_T and MIC and no dependence on the different β-lactamases expressed, it can be considered that this C_T of 0.5 mg/liter was sufficient to fully inhibit the β-lactamases in each of the isolates.

Determination of the avibactam PK/PD target when combined with ceftazidime against *P. aeruginosa*. A series of dose fractionation studies in neutropenic mouse thigh and lung infection models was used to define the PK/PD index of avibactam in combination with ceftazidime against ceftazidime-resistant *P. aeruginosa* isolates (44). In these experiments, dose fractionation was used to determine which PD index best described the PD of avibactam in combination with ceftazidime. The isolates used in these studies were tested with ceftazidime-avibactam MICs ranging from 2 to 16 mg/liter and produced AmpC β-lactamase (Tables 1, 2, and 3). Before the dose fractionation experiments were undertaken, it was necessary to establish a dose of

TABLE 2 Magnitudes of avibactam exposures associated with stasis and killing of *P. aeruginosa* in the neutropenic mouse thigh infection model in the background of q2h dosing of ceftazidime[a]

	MIC (mg/liter)			Avibactam %*f*T>1 mg/liter[c] yielding:	
Strain[b]	CAZ[d]	CAZ-AVI[e]	Expt[f]	Stasis	1-log$_{10}$ kill
1	128	8	Codosing	37.2	65.7
5	128	8	Codosing	14.1	32.9
7	64	4	AVI fractionation	74.1	Not reported
			Codosing	50.4	65.3
11	128	16	Codosing	29.1	37.5
18	32	2	AVI fractionation	30.2	Not reported
			Codosing	24.2	33.2
19	64	4	Codosing	62.5	67.2
Mean				40.2	50.3
SD				20	17

[a]Data were retabulated from Berkhout et al. (44).
[b]Resistance summaries for the strains used in this experiment are as follows. Strain 1, nitrocefinase activity, ++; AmpC transcript, overexpressed; β-lactamase genotype, *bla*$_{AmpC}$; class A$^-$, class B$^-$; strain 5: nitrocefinase activity, ++++; AmpC transcript, overexpressed; β-lactamase genotype, *bla*$_{AmpC}$; class A$^-$, class B$^-$; strain 7: nitrocefinase activity, +++; AmpC transcript, overexpressed; β-lactamase genotype, *bla*$_{AmpC}$; class A$^-$, class B$^-$; strain 11: OprD$^-$, AmpC^{con}, class A$^-$, class B$^-$; strain 18: OprD$^-$, AmpC$_{ind}$?, class A$^-$, class B$^-$; strain 19: OprD$^-$, AmpC^{con}, class A$^-$, class B$^-$.
[c]Times are expressed as the percentages of the dosing interval.
[d]CAZ, ceftazidime.
[e]AVI, avibactam.
[f]Codosing, ceftazidime and avibactam were codosed but the amount of avibactam was varied, without fractionating any given total daily dose; AVI fractionation, avibactam dose fractionation experiments.

TABLE 3 Magnitudes of avibactam exposures associated with stasis and bacterial killing of ceftazidime-resistant *P. aeruginosa* in the neutropenic mouse lung infection model in the background of q2h dosing of ceftazidime[a]

Strain[b]	MIC (mg/liter)		Codosing expt[e]	Avibactam %*f*T>1 mg/liter[f] associated with:		
	CAZ[c]	CAZ-AVI[d]		Stasis	1-$\log_{10}$ kill	2-$\log_{10}$ kill
5	128	8	q2h	19.4	20.6	Not reported
7	64	4	q2h	21.4	22.4	Not reported
11	128	16	q2h	19.7	34.9	55.3
			q8h	20.9	21.6	22.5
18	32	2	q2h	23.5	26.7	31.8
			q8h	16.1	17.8	20.2
Mean				20.2	24.0	32.4
SD				2.5	6.1	16

[a]Data are from Berkhout et al. (44).
[b]Resistance summaries for the strains used in this experiment are as follows. Strain 5: nitrocefinase activity, ++++; AmpC transcript, overexpressed; β-lactamase genotype, bla_{AmpC}; class A$^-$, class B$^-$; strain 7: nitrocefinase activity, +++; AmpC transcript, overexpressed; β-lactamase genotype, bla_{AmpC}; class A$^-$, class B$^-$; strain 11: OprD$^-$, AmpC^{con}, class A$^-$, class B$^-$; strain 18: OprD$^-$, AmpC$_{ind}$?, class A$^-$, class B$^-$; strain 19: OprD$^-$, AmpC^{con}, class A$^-$, class B$^-$.
[c]CAZ, ceftazidime.
[d]AVI, avibactam.
[e]q2h, ceftazidime and avibactam were dosed together at every administration; q8h, ceftazidime was dosed q2h but avibactam was codosed at 0, 8, and 16 h from the initiation of dosing.
[f]Times are expressed as percentages of the dosing interval.

ceftazidime monotherapy against each bacterial strain that would just allow maximal growth in the neutropenic mouse model. The concept was to establish the ceftazidime dose response of the system at a point whereby any reduction in bacterial growth was the result of β-lactamase inhibition by avibactam, restoring the activity of ceftazidime against the resistant strain. This approach enabled the determination of dose-response curves for avibactam when it was administered in the presence of ceftazidime dosed every 2 h (q2h) at the amount determined empirically for that strain, as described above.

The doses of avibactam were fractionated in the background of this specific q2h dosing schedule of ceftazidime, with responses measured as $\log_{10}$ change in CFU (44). The responses were plotted as a function of the PD indices *f*AUC, fC_{max}, and $fT{>}C_T$ for avibactam to determine which of these best correlated with antibacterial efficacy for ceftazidime-avibactam. For $fT{>}C_T$, the responses were plotted against three values of C_T, covering a 16-fold range: 0.25 mg/liter, 1 mg/liter, and 4 mg/liter. An example dose fractionation experiment for one of the *P. aeruginosa* strains is shown in Fig. 2. There was no significant relationship between the response to ceftazidime-avibactam and the avibactam C_{max}, suggesting that C_{max} was not the driver of efficacy. However, both $\%fT{>}C_T$ and AUC values of avibactam showed reasonable correlations with efficacy.

A subsequent experiment in the lung infection model tested the hypothesis that $\%fT{>}C_T$ was a more predictive avibactam index than AUC (44). Identical daily doses of avibactam were given either q2h or q8h in the background of the q2h dosing schedule of ceftazidime described above. The two widely different dose intervals were selected to gather more data points and increase the ability to distinguish between AUC and time as PK/PD indices. The avibactam static total daily doses and $\%fT{>}C_T$ values required for stasis in two isolates of *P. aeruginosa* are summarized in Table 1. The total daily dose of avibactam that resulted in a static effect was lower for the more frequent q2h dosing of avibactam than for q8h dosing in both strains of ceftazidime-resistant *P. aeruginosa* (by factors of 10.1 and 2.7) (Table 1) (44). Despite this difference in total daily dose, the values of $\%fT{>}C_T$ of 1 mg/liter that yielded stasis from the two avibactam dosing frequencies were similar (16.1 and 23.5%) (Table 1). These results were consistent with the hypothesis that the PD of avibactam in restoring the antibacterial activity of ceftazidime in ceftazidime-resistant *P. aeruginosa* was time dependent rather than concentration dependent (i.e., linked to $fT{>}$concentration [C_T] rather than *f*AUC).

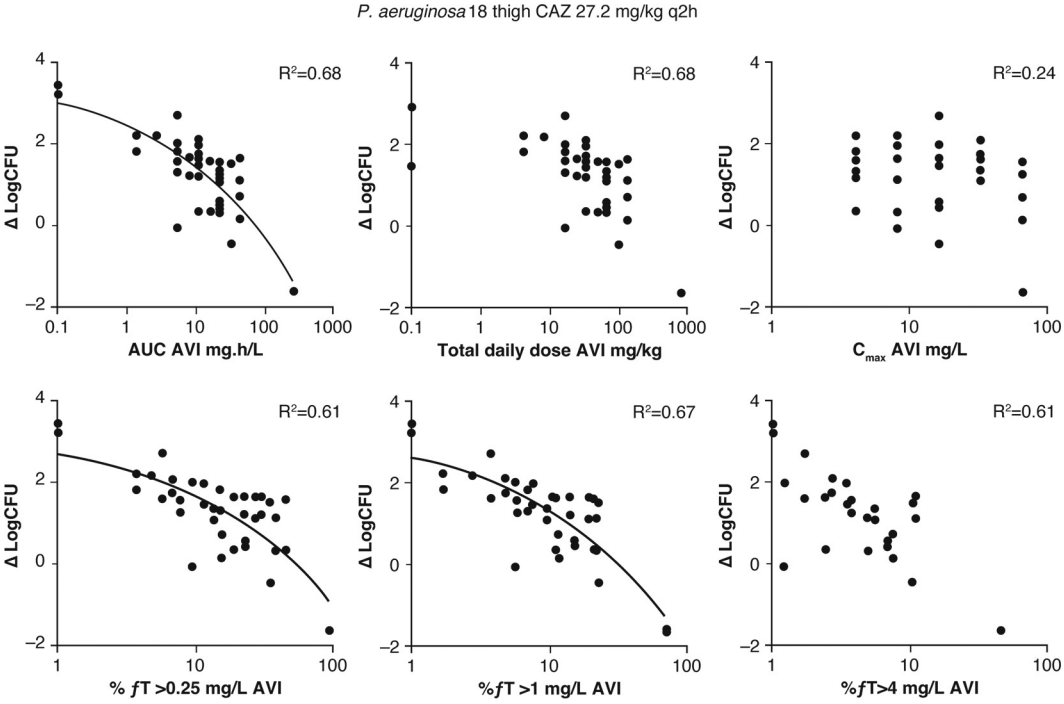

FIG 2 Dose fractionation study of avibactam in combination with ceftazidime against a ceftazidime-resistant *P. aeruginosa* strain in the neutropenic mouse thigh infection model. AVI, avibactam; CAZ, ceftazidime; ΔlogCFU, change in $\log_{10}$ CFU compared to the initial inoculum. Republished from reference 44.

Results from similar experiments in the thigh infection model showed a significant relationship between an increased frequency of dosing and a change in $\log_{10}$ CFU for similar avibactam total daily doses, confirming the importance of %fT>C_T in the PD of avibactam (44). A C_T of 1 mg/liter was chosen as the reference concentration, because in the dose fractionation study, higher r^2 coefficients were found for the association between the PD effect of avibactam (change in log CFU) and %fT>C_T 1 mg/liter than for %fT>C_T 0.25 mg/liter and %fT>C_T 4 mg/liter (r^2 0.67 versus 0.61 and 0.61, respectively).

Having chosen the reference concentration of avibactam, further ceftazidime-avibactam codosing experiments were conducted with four *P. aeruginosa* strains in the lung model and six strains in the thigh model to determine the relationship between the magnitude of %fT>C_T 1 mg/liter and the magnitude of the PD effect. The %fT>C_T 1 mg/liter values that yielded PD effects of net stasis and a 1-$\log_{10}$ kill in the neutropenic mouse thigh infection model for the different *P. aeruginosa* strains are shown in Table 2, while those derived from the lung model, including the %fT>C_T 1 mg/liter that yielded a 2-$\log_{10}$ kill, are shown in Table 3. The mean exposure that yielded 1-$\log_{10}$ killing of *P. aeruginosa* in the neutropenic mouse thigh model (50.3%) was equivalent to the avibactam exposure target of approximately 50% fT>C_T of 1 mg/liter. Moreover, this target exceeded the avibactam exposure of 40% fT>C_T of 1 mg/liter that was associated with bacterial stasis (Table 2). In addition, the avibactam target of 50% fT>C_T of 1 mg/liter exceeded the exposures associated with stasis, 1-$\log_{10}$ kill, and 2-$\log_{10}$ kill of *P. aeruginosa* in the neutropenic mouse lung infection model (Table 3). Again, in these sets of experiments where the ceftazidime-avibactam MIC ranged from 2 to 16 mg/liter, there was no noticeable correlation between the avibactam C_T and MIC or the level of β-lactamase expressed.

On the basis of these experiments, %fT>C_T was determined as the PK/PD index that was best associated with the restoration of ceftazidime efficacy by avibactam in the neutropenic mice thigh and lung infection models. The most appropriate C_T value of avibactam associated with efficacy against ceftazidime-resistant *P. aeruginosa* was 1 mg/liter.

Ceftazidime-avibactam PK/PD targets used to support dosage selection. Joint PTA analyses based on the simultaneous achievement of both the ceftazidime and avibactam PK/PD targets in ≥90% of patients have subsequently been used to support ceftazidime-avibactam dosage selection (45). The ceftazidime-avibactam dose was designed to provide adequate target attainment in ≥90% of patients in whom the infecting organism would respond in a susceptibility test with a ceftazidime-avibactam MIC of 8 mg/liter. The ceftazidime-avibactam MIC value of 8 mg/liter was chosen as the cutoff for assessing PTA on the basis of reported ceftazidime-avibactam MIC_{90} values from global surveillance data for *Enterobacteriaceae* and *P. aeruginosa*, as described above (36–42). Therefore, we propose that the approach to dosage selection based on ≥90% of patients attaining ceftazidime exposures adequate to treat infecting bacteria against which the ceftazidime-avibactam MIC would be 8 mg/liter is conservative, because the PTA is based on the 90th percentile MIC of the MIC frequency distribution of clinical isolates as opposed to the whole distribution. That is, in patients infected by most examples of *Enterobacteriaceae* or *P. aeruginosa* and dosed with ceftazidime-avibactam, the ceftazidime PK/PD target is predicted to be well exceeded.

The avibactam exposure target of $fT>C_T$ of 1 mg/liter for at least 50% of the dosing interval was chosen for determining the PTA for avibactam in combination with ceftazidime. This also matched the exposure target for ceftazidime (50% $fT >$ ceftazidime-avibactam MIC of 8 mg/liter) (45–48). The C_T of 1 mg/liter value was regarded as an adequate index for analyses of PK/PD target attainment against *P. aeruginosa* on the basis of the neutropenic mouse thigh and lung infection studies and as a conservative index for analyses of PK/PD target attainment against *Enterobacteriaceae*, as C_T and C_T[Q8] were estimated to be ≤0.5 mg/liter in the *in vitro* hollow-fiber studies by Coleman and colleagues (43). The experiments included a range of different isolates with differing β-lactamase expressions and a clinically relevant ceftazidime-avibactam MIC range. In both the *in vitro* and *in vivo* sets of experiments, there was no relationship between C_T and either MIC or the identity of the β-lactamases tested, demonstrating that the C_T of 1 mg/liter sufficiently inhibits all β-lactamase expression in the isolates tested. Thus, the avibactam PK/PD target of C_T of 1 mg/liter was considered appropriate to use together with the ceftazidime PK/PD target in joint PTA analyses for ceftazidime-avibactam dosage selection.

AVIBACTAM PK/PD INDEX AND TARGET IN COMBINATION WITH AZTREONAM

Singh and colleagues (49) used an *in vitro* hollow-fiber model and a neutropenic mouse infection model to investigate the PK/PD indices and magnitudes for aztreonam and avibactam in combination against *Enterobacteriaceae* (49). Six aztreonam-resistant *Enterobacteriaceae* isolates (three *K. pneumoniae* and three *Escherichia coli*) all coproducing an MBL and an ESBL and/or a class C β-lactamase (CMY type) were used in these experiments. The MIC values of aztreonam-avibactam against these isolates ranged from 0.125 to 8 mg/liter. Two sets of hollow-fiber experiments were performed; the first evaluated the PK/PD index of aztreonam in the presence of avibactam and the second evaluated the PK/PD index and magnitude of avibactam in the presence of a fixed dose of aztreonam. The avibactam PK/PD target derived from the hollow-fiber experiments was then validated in a neutropenic mouse thigh infection model.

The first set of hollow-fiber experiments was designed to evaluate whether the aztreonam PK/PD index changed with the addition of avibactam (49). In these experiments, avibactam at 4 mg/liter was continuously infused in combination with different dosage regimens of aztreonam, and the responses of two of the *Enterobacteriaceae* isolates were measured. As was inferred for ceftazidime, the PK/PD index that best correlated with the efficacy of aztreonam in combination with avibactam was $\%fT>MIC$ of the combination. The magnitude of the index associated with a 1-$\log_{10}$ kill over 24 h was 50 to 55%. These initial experiments demonstrated that the aztreonam PK/PD index was not changed by the presence of avibactam and that the magnitudes associated with activity against aztreonam-resistant bacteria in the presence of avibactam were as expected for a β-lactam against susceptible bacteria.

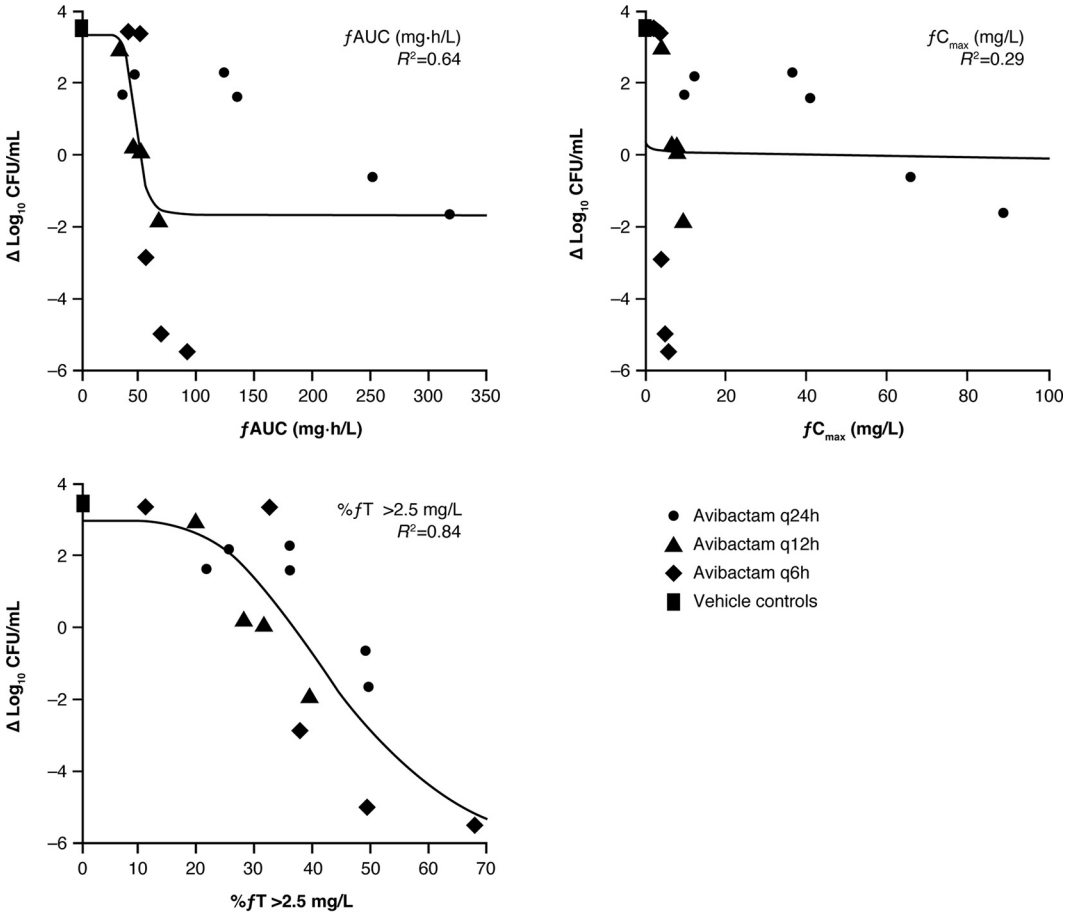

FIG 3 PK/PD relationship between *f*AUC, fC_{max}, and %*f*T>C_T for avibactam in the presence of fixed dosing of aztreonam against an *E. coli* strain in the hollow-fiber model. Symbols represent experimental observations for different dosage regimens of avibactam and continuous lines represent the predicted best-fit model. Republished from reference 49 with permission from the British Society for Antimicrobial Chemotherapy.

In the second set of hollow-fiber studies, a fixed dose of aztreonam was administered every 6 h to simulate a human-like PK profile in the presence of different dosage regimens of avibactam (49). As the previous experiments had shown that 50% *f*T>MIC was sufficient for aztreonam efficacy in the presence of avibactam against *Enterobacteriaceae*, the fixed aztreonam dose was therefore designed to provide 50 to 100% *f*T>MIC against the isolate under study. An example dose fractionation experiment of avibactam in combination with aztreonam against one of the *E. coli* strains is shown in Fig. 3. From these dose fractionation experiments, the effect of avibactam in restoring the antibacterial activity of aztreonam was found to correlate best with %*f*T>C_T. The PK/PD indices *f*AUC and fC_{max} were also analyzed but did not correlate well with response. The magnitude of C_T that best correlated with efficacy was evaluated for C_T values ranging from 0.5 to 4 mg/liter. For five of the six isolates, a C_T of 2.5 mg/liter provided the best fit; for these isolates (two *K. pneumoniae* and three *E. coli*), the mean value of %*f*T>C_T of 2.5 mg/liter that yielded a 1-$\log_{10}$ kill was 47.5% (range, 40.9 to 58.2%) (Table 4). In the other *K. pneumoniae* isolate, a C_T of 2 mg/liter provided a better correlation, with a value of 38% *f*T>C_T yielding a 1-$\log_{10}$ kill. As the efficacy best correlated with a C_T of 2.5 mg/liter in five of the six isolates tested, this threshold value was chosen for use in PTA analyses for dosage selection. As with the ceftazidime-avibactam experiments described above, there was no relationship between the C_T and aztreonam-avibactam MIC or β-lactamase expression.

The bacterial responses associated with these avibactam exposure magnitudes were confirmed in further dose fractionation experiments in the neutropenic mouse thigh

TABLE 4 Magnitudes of avibactam exposures associated with stasis and killing of metallo-β-lactamase- and ESBL- and/or CMY-type β-lactamase-coproducing isolates of *K. pneumoniae* and *E. coli* in the background of 6-hourly dosing of aztreonam over 24 h in a hollow-fiber model *in vitro*[a]

	Avibactam %*f*T>2.5 mg/liter[c] yielding:	
Strain[b]	Stasis	1-$\log_{10}$ kill
K. pneumoniae ARC3602	39.3	46.1
K. pneumoniae ARC3803	41.8	44.3
E. coli ARC3600	36.1	40.9
E. coli ARC3805	56.4	58.2
E. coli ARC3807	43.2	48.1
Mean	43.4	47.5
SD	7.8	6.5

[a]Data were retabulated from Singh et al. (49) with permission from the British Society for Antimicrobial Chemotherapy. ESBL, extended-spectrum β-lactamase.
[b]*K. pneumoniae* ARC3802 omitted because only bacterial responses correlating with an *f*T>2 mg/liter were reported for that isolate.
[c]Times are expressed as percentages of the 24-h period of the experiment.

(49) and lung (our unpublished data) infection models. In the thigh infection model, four-hourly codosing of aztreonam and avibactam (4:1 by weight) provided aztreonam 70 to 100% *f*T>MIC of the combination. With the aztreonam exposures set to >50% *f*T>MIC, the efficacy of aztreonam-avibactam correlated with avibactam %*f*T>C_T of 2 to 2.5 mg/liter. Twenty-four-hour stasis was achieved against an *E. coli* isolate at 23% *f*T>C_T 2.5 mg/liter and against a *K. pneumoniae* isolate at 25% *f*T>C_T 2 mg/liter. The maximal effect of avibactam was achieved at 35 to 40% *f*T>C_T 2 to 2.5 mg/liter for both isolates, which was consistent with the results observed in the hollow-fiber model experiments.

These studies showed that, as had been found for ceftazidime, the PK/PD index that best correlated with the restoration of the antibacterial activity of aztreonam by avibactam was %*f*T>C_T. In both the hollow-fiber and neutropenic mouse infection models, a C_T value of 2.5 mg/liter for avibactam correlated best with the restoration of aztreonam efficacy against aztreonam-resistant *Enterobacteriaceae*. On the basis of these results, PK/PD targets of aztreonam 60% *f*T>MIC for aztreonam-avibactam and avibactam 50% *f*T>C_T of 2.5 mg/liter were considered appropriate for PTA analyses to guide dosage selection for aztreonam-avibactam (our unpublished data).

PK/PD STUDIES OF AVIBACTAM IN COMBINATION WITH CEFTAROLINE IN AN *IN VITRO* HOLLOW-FIBER MODEL

Louie and colleagues (50) used a hollow-fiber model to analyze the PK/PD index of avibactam in combination with ceftaroline against two *K. pneumoniae* isolates (one expressing KPC-2, SHV-27, and TEM-1 and the other expressing CTX-M-15) and against an *E. cloacae* isolate expressing stably derepressed AmpC. In the first set of experiments, different doses of avibactam were administered as a continuous infusion in the presence of ceftaroline concentrations simulating human PK profiles following a dose of 600 mg q8h. These dose-ranging experiments enabled an identification of the effective 24-h AUC for avibactam, which informed the design of the dose fractionation experiments to identify the avibactam PK/PD index (50).

For the dose fractionation experiments, different dosage regimens of avibactam were given together with ceftaroline 600 mg q8h (50). In these experiments, each avibactam dosage regimen was designed to generate approximately the same 24-h AUC as that provided by an avibactam continuous infusion of 8 mg/liter (24-h AUC of 192 mg · h/liter). Four regimens of avibactam in combination with ceftaroline were administered: avibactam given as a continuous infusion, the whole exposure administered once daily, half the exposure administered twice daily, and one third of the total exposure administered q8h. One major difference between the studies of avibactam in combination with ceftaroline and those of the combination with ceftazidime or aztreonam was that instead of 24-h killing and the prevention of growth, the endpoint of the

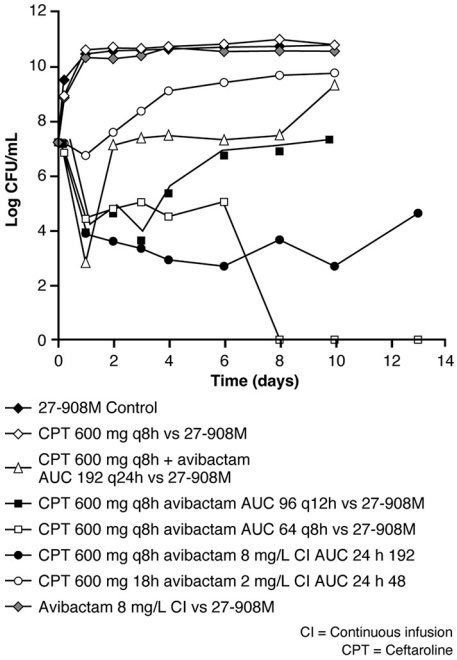

FIG 4 Dose fractionation study for avibactam in combination with ceftaroline 600 mg q8h against a *K. pneumoniae* strain in the hollow-fiber model. AUC, area under the concentration-time curve. Republished from reference 50.

ceftaroline studies was the maintenance of a reduced bacterial CFU/ml and the prevention of outgrowth of resistant variants over 10 or 13 days (50). In dose fractionation experiments with *K. pneumoniae* expressing KPC-2, SHV-27, and TEM-1 (Fig. 4), the administration of the avibactam total daily dose (as a single dose) once daily failed by day 2 of treatment. Moreover, giving one half of the avibactam total daily dose every 12 h failed by day 4. In contrast, the more fractionated schedules of avibactam administration (where avibactam was given q8h or as a continuous infusion over 24 h) were successful in suppressing the emergence of resistance for the duration of the experiment (Fig. 4). Similar results were achieved with dose fractionation experiments using the *K. pneumoniae* CTX-M-15 isolate or the *E. cloacae* isolate. As the more fractionated avibactam dosage regimens maximized the time above the threshold concentration, these experiments showed that the activity of avibactam in combination with ceftaroline was clearly linked to $fT{>}C_T$ more closely than it was to *f*AUC (50).

PK/PD STUDIES OF AVIBACTAM IN COMBINATION WITH CEFTAROLINE OR CEFTAZIDIME IN A SINGLE-COMPARTMENT CONSTANT-VOLUME FERMENTER MODEL *IN VITRO*

MacGowan and colleagues (51) fractionated doses of avibactam combined with constant q8h dosing of either ceftazidime or ceftaroline in a one-compartment *in vitro* PK/PD model against each of three ceftazidime- and ceftaroline-resistant β-lactamase-producing isolates of *Enterobacteriaceae* (CTX-M-type-producing *E. coli*, stably derepressed AmpC-producing *E. cloacae*, and KPC-type-producing *K. pneumoniae*). Unlike the results of the hollow-fiber studies and neutropenic mouse models described above, the activity of avibactam in potentiating the bacterial killing by ceftazidime and ceftaroline over 24 h more closely fit the PK/PD indices *f*AUC and fC_{max} than the index $fT{>}C_T$. The authors proposed that different experimental designs might produce differently distributed data. It was suggested that the greater number of observations at 0% $fT{>}C_T$ and 100% $fT{>}C_T$ in these experiments could have resulted in a better correlation to AUC and C_{max} rather than the time above the threshold, in contrast to the other experiments described above which had fewer observations at the extremes. This potentially explains the different conclusions from this model compared with those

TABLE 5 PK/PD indices for avibactam acting in combination with β-lactams under conditions of dynamic rising and falling concentration-time curves

β-Lactamase inhibitor	β-Lactam	Model	Period (days)	Derived PK/PD index	Reference
Avibactam	Ceftazidime	Hollow fiber; enterics[a]	1	$C_T \geq 0.5$ mg/liter maintained β-lactamase-null phenotype	43
Avibactam	Ceftazidime	Neutropenic mouse thigh; *P. aeruginosa*	1	$fT>C_T$ 1 mg/liter	44
Avibactam	Ceftazidime	Neutropenic mouse lung; *P. aeruginosa*	1	$fT>C_T$ 1 mg/liter	44
Avibactam	Aztreonam	Hollow fiber; enterics	1	$fT>C_T$ 2–2.5 mg/liter	49
Avibactam	Aztreonam	Neutropenic mouse thigh; enterics	1	$fT>C_T$ 2–2.5 mg/liter	49
Avibactam	Ceftaroline	Hollow fiber; enterics	10–13	$fT>C_T$	50
Avibactam	Ceftazidime	Constant-volume fermenter; enterics	1	*f*AUC	51
Avibactam	Ceftaroline	Constant-volume fermenter; enterics	1	*f*AUC	51

[a]Enterics, *Enterobacteriaceae*.

from the other studies with avibactam combinations, all of which concluded that the avibactam $fT>C_T$ was the more closely fitting PK/PD index for avibactam than *f*AUC (51).

COMPARISON BETWEEN MODELS AND AVIBACTAM COMBINATIONS

Table 5 summarizes the PK/PD indices that best fit avibactam in the studies discussed above. For each combination, concentration-time profiles simulating predicted concentrations in human patients following dosing with clinically achievable regimens were studied in hollow-fiber models. Dose fractionation experiments were also conducted in neutropenic mice infection models for the ceftazidime-avibactam and aztreonam-avibactam combinations and in an *in vitro* single-compartment constant-volume fermenter model for ceftazidime-avibactam and ceftaroline fosamil-avibactam. Despite the different endpoints and durations of the experiments, in most of the models and across all the β-lactam combinations, there was an optimal fit between PD effect and avibactam $fT>C_T$. The magnitude of C_T varied between 0.5 mg/liter and 2.5 mg/liter depending on the model and the partner β-lactam. It is not unexpected for the C_T of avibactam to be different depending on the partner β-lactam; therefore, it is important to study PK/PD indices for each different combination. The only exception has been that in the single-compartment fermenter model in which combinations of ceftazidime and ceftaroline (but not aztreonam) were studied, a better fit was obtained between the activity of avibactam and the index *f*AUC (and fC_{max}) than between the activity of avibactam and $fT>C_T$ in restoring the activities of both of these β-lactams (51). As discussed above, this could be a function of the experimental conditions in this particular analysis which resulted in a clustering of "time above" parameters at the extremes.

CLINICAL CONTEXT

The PKs of avibactam in combination with ceftazidime have been well characterized in population PK models developed using patient PK data from the ceftazidime-avibactam phase 3 studies (52). Joint target attainment was calculated using the models such that PTA was based on each patient achieving both the ceftazidime and avibactam targets simultaneously. From these models, the ceftazidime and avibactam PK/PD target plasma concentrations of >8 mg/liter for ceftazidime and >1 mg/liter for avibactam for more than 50% of the dosing interval have been predicted to be achieved in over 90% of patients dosed with ceftazidime-avibactam 2,000 mg + 500 mg q8h (52). These calculations of joint PTA supported ceftazidime-avibactam dosage selection and clinical breakpoint analyses (45).

The efficacy of the selected ceftazidime-avibactam dosage regimen with respect to comparators has been demonstrated across five phase 3 clinical trials, including a study which included only patients with infections caused by ceftazidime-resistant pathogens (53–57). It is important to consider whether antibiotic dosing strategies are adequate for the suppression of resistance in key target pathogens. Although the evidence for the emergence of resistance to ceftazidime-avibactam is limited, there have been

isolated reports of the development of ceftazidime-avibactam resistance in some KPC-producing *K. pneumoniae* (58). *In vitro* models can be used to help identify PK/PD targets predicted to minimize the risk of selecting for resistance to the antibiotic in patients (19). This has been investigated for ceftaroline fosamil-avibactam (50) but not for ceftazidime-avibactam or aztreonam-avibactam.

CONCLUSIONS

The primary reason for conducting nonclinical PK/PD studies for antibiotics is to define quantitative PK/PD exposure targets that can be used to analyze the PTA among simulated populations of patients and thus guide the selection of appropriate doses for assessment in phase 2 and 3 clinical trials. For β-lactam–β-lactamase inhibitor combinations, it is important to determine the PK/PD index and magnitude for both components, as described here for avibactam in combination with the β-lactams ceftazidime, aztreonam, and ceftaroline fosamil. Across all combinations, with the exception of one experimental model in which combinations of ceftazidime or ceftaroline fosamil with avibactam were investigated (51), the PD of avibactam in restoring the antibacterial activity of the three partner β-lactams was found to be time dependent rather than concentration dependent (i.e., linked to $f\mathrm{T}>\mathrm{C_T}$ rather than fAUC). The magnitude of $\mathrm{C_T}$ varied depending on the model and the partner β-lactam, emphasizing the importance of studying PK/PD indices for each different β-lactam–β-lactamase inhibitor combination. For ceftazidime-avibactam, PTA analyses based on the achievement of the preclinical PK/PD targets described here were used to guide the selection of ceftazidime-avibactam dosage regimens used in phase 3 clinical trials, which have demonstrated clinical efficacy similar to that of carbapenems in patients with cIAI, cUTI, and nosocomial pneumonia, including those with infections caused by ceftazidime-resistant pathogens (53–57).

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REFERENCES

1. Mager DE, Woo S, Jusko WJ. 2009. Scaling pharmacodynamics from in vitro and preclinical animal studies to humans. Drug Metab Pharmacokinet 24:16–24. https://doi.org/10.2133/dmpk.24.16.
2. Bueters T, Gibson C, Visser SA. 2015. Optimization of human dose prediction by using quantitative and translational pharmacology in drug discovery. Future Med Chem 7:2351–2369. https://doi.org/10.4155/fmc.15.143.
3. Felmlee MA, Morris ME, Mager DE. 2012. Mechanism-based pharmacodynamic modeling. Methods Mol Biol 929:583–600. https://doi.org/10.1007/978-1-62703-050-2_21.
4. Lee JY, Garnett CE, Gobburu JV, Bhattaram VA, Brar S, Earp JC, Jadhav PR, Krudys K, Lesko LJ, Li F, Liu J, Madabushi R, Marathe A, Mehrotra N, Tornoe C, Wang Y, Zhu H. 2011. Impact of pharmacometric analyses on new drug approval and labelling decisions: a review of 198 submissions between 2000 and 2008. Clin Pharmacokinet 50:627–635. https://doi.org/10.2165/11593210-000000000-00000.
5. Sundqvist M, Lundahl A, Nagard MB, Bredberg U, Gennemark P. 2015. Quantifying and communicating uncertainty in preclinical human dose-prediction. CPT Pharmacometrics Syst Pharmacol 4:243–254. https://doi.org/10.1002/psp4.32.
6. Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, Drusano GL. 2007. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis 44:79–86. https://doi.org/10.1086/510079.
7. Ehmann DE, Jahic H, Ross PL, Gu RF, Hu J, Durand-Reville TF, Lahiri S, Thresher J, Livchak S, Gao N, Palmer T, Walkup GK, Fisher SL. 2013. Kinetics of avibactam inhibition against class A, C, and D β-lactamases. J Biol Chem 288:27960–27971. https://doi.org/10.1074/jbc.M113.485979.
8. Sader H, Castanheira M, Mendes RE, Flamm RK, Farrell DJ, Jones RN. 2015. Ceftazidime-avibactam activity against multidrug-resistant *Pseudomonas aeruginosa* isolated in U.S. medical centers in 2012 and 2013. Antimicrob Agents Chemother 59:3656–3659. https://doi.org/10.1128/AAC.05024-14.
9. Nichols WW, de Jonge BL, Kazmierczak KM, Karlowsky JA, Sahm DF.

2016. *In vitro* susceptibility of global surveillance isolates of *Pseudomonas aeruginosa* to ceftazidime-avibactam (INFORM 2012 to 2014). Antimicrob Agents Chemother 60:4743–4749. https://doi.org/10.1128/AAC.00220-16.
10. de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. 2016. *In vitro* susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible *Enterobacteriaceae* isolates collected during the INFORM global surveillance study (2012 to 2014). Antimicrob Agents Chemother 60:3163–3169. https://doi.org/10.1128/AAC.03042-15.
11. Allergan. 2018. AVYCAZ (ceftazidime-avibactam) for injection, for intravenous use. Prescribing information. http://www.allergan.com/assets/pdf/avycaz_pi. Accessed 7 February 2018.
12. Pfizer. 2016. ZAVICEFTA. Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf. Accessed 7 February 2018.
13. Livermore DM, Mushtaq S, Warner M, Zhang J, Maharjan S, Doumith M, Woodford N. 2011. Activities of NXL104 combinations with ceftazidime and aztreonam against carbapenemase-producing *Enterobacteriaceae*. Antimicrob Agents Chemother 55:390–394. https://doi.org/10.1128/AAC.00756-10.
14. Crandon JL, Nicolau DP. 2013. Human simulated studies of aztreonam and aztreonam-avibactam to evaluate activity against challenging Gram-negative organisms, including metallo-β-lactamase producers. Antimicrob Agents Chemother 57:3299–3306. https://doi.org/10.1128/AAC.01989-12.
15. Biedenbach DJ, Kazmierczak K, Bouchillon SK, Sahm DF, Bradford PA. 2015. *In vitro* activity of aztreonam-avibactam against a global collection of Gram-negative pathogens from 2012 and 2013. Antimicrob Agents Chemother 59:4239–4248. https://doi.org/10.1128/AAC.00206-15.
16. Castanheira M, Sader HS, Farrell DJ, Mendes RE, Jones RN. 2012. Activity of ceftaroline-avibactam tested against Gram-negative organism populations, including strains expressing one or more β-lactamases and methicillin-resistant *Staphylococcus aureus* carrying various staphylococcal cassette chromosome mec types. Antimicrob Agents Chemother 56:4779–4785. https://doi.org/10.1128/AAC.00817-12.
17. Pfizer 2017. NCT02655419. Determine the PK and safety and tolerability of ATM-AVI for the treatment of cIAIs in hospitalized adults (REJUVENATE). https://clinicaltrials.gov/ct2/show/NCT02655419. Accessed 7 February 2018.
18. Forest Laboratories. 2017. NCT01281462. Comparative study of co-administered ceftaroline fosamil and NXL104 vs. intravenous doripenem in adult subjects with complicated urinary tract infections. https://clinicaltrials.gov/ct2/show/NCT01281462. Accessed 7 February 2018.
19. European Medicines Agency. 2016. Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products. Document EMA/CHMP/594085/2015. European Medicines Agency, London, United Kingdom. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500210982.pdf. Accessed 7 February 2018.
20. Nielsen EI, Friberg LE. 2013. Pharmacokinetic-pharmacodynamic modeling of antibacterial drugs. Pharmacol Rev 65:1053–1090. https://doi.org/10.1124/pr.111.005769.
21. Rex JH, Goldberger M, Eisenstein BI, Harney C. 2014. The evolution of the regulatory framework for antibacterial agents. Ann N Y Acad Sci 1323:11–21. https://doi.org/10.1111/nyas.12441.
22. Mouton JW, Brown DF, Apfalter P, Canton R, Giske CG, Ivanova M, MacGowan AP, Rodloff A, Soussy CJ, Steinbakk M, Kahlmeter G. 2012. The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach. Clin Microbiol Infect 18:E37–E45. https://doi.org/10.1111/j.1469-0691.2011.03752.x.
23. Muller AE, Punt N, Mouton JW. 2013. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. J Antimicrob Chemother 68:900–906. https://doi.org/10.1093/jac/dks468.
24. Kuti JL, Nicolau DP. 2005. Making the most of surveillance studies: summary of the OPTAMA program. Diagn Microbiol Infect Dis 53:281–287. https://doi.org/10.1016/j.diagmicrobio.2005.10.004.
25. Dudley MN, Ambrose PG, Bhavnani SM, Craig WA, Ferraro MJ, Jones RN, Antimicrobial Susceptibility Testing Subcommittee of the Clinical and Laboratory Standards Institute. 2013. Background and rationale for revised Clinical and Laboratory Standards Institute interpretive criteria (breakpoints) for *Enterobacteriaceae* and *Pseudomonas aeruginosa*: I. Cephalosporins and aztreonam. Clin Infect Dis 56:1301–1309. https://doi.org/10.1093/cid/cit017.
26. Drusano GL. 2004. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol 2:289–300. https://doi.org/10.1038/nrmicro862.
27. Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. 2005. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother 55:601–607. https://doi.org/10.1093/jac/dki079.
28. Dudley MN. 1995. Combination β-lactam and β-lactamase-inhibitor therapy: pharmacokinetic and pharmacodynamic considerations. Am J Health Syst Pharm 52:S23–S28.
29. Andes D, Craig WA. 2002. Animal model pharmacokinetics and pharmacodynamics: a critical review. Int J Antimicrob Agents 19:261–268. https://doi.org/10.1016/S0924-8579(02)00022-5.
30. Craig WA. 2003. Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 17:479–501. https://doi.org/10.1016/S0891-5520(03)00065-5.
31. Craig WA. 2007. Pharmacodynamics of antimicrobials: general concepts and applications, p 1–19. *In* Nightingale CH, Ambrose PG, Drusano GL, Murakawa T (ed), Antimicrobial pharmacodynamics in theory and clinical practice, 2nd ed. Informa Healthcare, New York, NY.
32. MacVane SH, Kuti JL, Nicolau DP. 2014. Clinical pharmacodynamics of antipseudomonal cephalosporins in patients with ventilator-associated pneumonia. Antimicrob Agents Chemother 58:1359–1364. https://doi.org/10.1128/AAC.01463-13.
33. DeRyke CA, Kuti JL, Nicolau DP. 2007. Reevaluation of current susceptibility breakpoints for Gram-negative rods based on pharmacodynamic assessment. Diagn Microbiol Infect Dis 58:337–344. https://doi.org/10.1016/j.diagmicrobio.2007.01.004.
34. Frei CR, Wiederhold NP, Burgess DS. 2008. Antimicrobial breakpoints for Gram-negative aerobic bacteria based on pharmacokinetic-pharmacodynamic models with Monte Carlo simulation. J Antimicrob Chemother 61:621–628. https://doi.org/10.1093/jac/dkm536.
35. EUCAST. 2010. Ceftazidime. Rationale for the EUCAST clinical breakpoints, version 1.0. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Ceftazidime_Rationale_Document_1.0_2010Nov.pdf. Accessed 7 February 2018.
36. Flamm RK, Stone GG, Sader HS, Jones RN, Nichols WW. 2014. Avibactam reverts the ceftazidime MIC90 of European Gram-negative bacterial clinical isolates to the epidemiological cut-off value. J Chemother 26:333–338. https://doi.org/10.1179/1973947813Y.0000000145.
37. Sader H, Castanheira M, Flamm RK, Farrell DJ, Jones RN. 2014. Antimicrobial activity of ceftazidime-avibactam against Gram-negative organisms collected from U.S. medical centers in 2012. Antimicrob Agents Chemother 58:1684–1692. https://doi.org/10.1128/AAC.02429-13.
38. Levasseur P, Girard A-M, Claudon M, Goossens H, Black MT, Coleman K, Miossec C. 2012. *In vitro* antibacterial activity of the ceftazidime-avibactam (NXL104) combination against *Pseudomonas aeruginosa* clinical isolates. Antimicrob Agents Chemother 56:1606–1608. https://doi.org/10.1128/AAC.06064-11.
39. Walkty A, DeCorby M, Lagacé-Wiens P, Karlowsky J, Hoban D, Zhanel G. 2011. *In vitro* activity of ceftazidime combined with NXL104 versus *Pseudomonas aeruginosa* isolates obtained from patients in Canadian hospitals (CANWARD 2009 study). Antimicrob Agents Chemother 55:2992–2994. https://doi.org/10.1128/AAC.01696-10.
40. Wang X, Zhang F, Zhao C, Wang Z, Nichols WW, Testa R, Li H, Chen H, He W, Wang Q. 2014. *In vitro* activity of ceftazidime-avibactam and aztreonam-avibactam against 372 Gram-negative bacilli collected in 2011 and 2012 from 11 teaching hospitals in China. Antimicrob Agents Chemother 58:1774–1778. https://doi.org/10.1128/AAC.02123-13.
41. Reference deleted.
42. Castanheira M, Farrell SE, Krause KM, Jones RN, Sader HS. 2014. Contemporary diversity of beta-lactamases among *Enterobacteriaceae* in the nine U.S. census regions and ceftazidime-avibactam activity tested against isolates producing the most prevalent beta-lactamase groups. Antimicrob Agents Chemother 58:833–838. https://doi.org/10.1128/AAC.01896-13.
43. Coleman K, Levasseur P, Girard AM, Borgonovi M, Miossec C, Merdjan H, Drusano G, Shlaes D, Nichols WW. 2014. Activities of ceftazidime and avibactam against β-lactamase-producing *Enterobacteriaceae* in a hollow-fiber pharmacodynamic model. Antimicrob Agents Chemother 58:3366–3372. https://doi.org/10.1128/AAC.00080-14.

44. Berkhout J, Melchers MJ, van Mil AC, Seyedmousavi S, Lagarde CM, Schuck VJ, Nichols WW, Mouton JW. 2016. Pharmacodynamics of ceftazidime and avibactam in neutropenic mice with thigh or lung infection. Antimicrob Agents Chemother 60:368–375. https://doi.org/10.1128/AAC.01269-15.
45. European Medicines Agency. 2016. Zavicefta. European public assessment report. European Medicines Agency, London, United Kingdom. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004027/WC500210236.pdf. Accessed 7 February 2018.
46. Cerexa, Inc. 2014. Briefing package, NDA 206494: ceftazidime-avibactam. Cerexa, Inc., Alameda, CA. https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Pink%20Sheet%20DAILY/2014/December/12314%20FDA%20briefing%20docs.pdf.
47. Nicolau DP. 2015. Focus on ceftazidime-avibactam for optimizing outcomes in complicated intra-abdominal and urinary tract infections. Expert Opin Investig Drugs 24:1261–1273. https://doi.org/10.1517/13543784.2015.1062873.
48. Mawal Y, Critchley IA, Riccobene TA, Talley AK. 2015. Ceftazidime-avibactam for the treatment of complicated urinary tract infections and complicated intra-abdominal infections. Expert Rev Clin Pharmacol 8:691–707. https://doi.org/10.1586/17512433.2015.1090874.
49. Singh R, Kim A, Tanudra MA, Harris JJ, McLaughlin RE, Patey S, O'Donnell JP, Bradford PA, Eakin AE. 2015. Pharmacokinetics/pharmacodynamics of a β-lactam and β-lactamase inhibitor combination: a novel approach for aztreonam/avibactam. J Antimicrob Chemother 70:2618–2626. https://doi.org/10.1093/jac/dkv132.
50. Louie A, Castanheira M, Liu W, Grasso C, Jones RN, Williams G, Critchley I, Thye D, Brown D, Vanscoy B, Kulawy R, Drusano GL. 2012. Pharmacodynamics of β-lactamase inhibition by NXL104 in combination with ceftaroline: examining organisms with multiple types of β-lactamases. Antimicrob Agents Chemother 56:258–270. https://doi.org/10.1128/AAC.05005-11.
51. MacGowan A, Tomaselli S, Noel A, Bowker K. 2017. The pharmacodynamics of avibactam in combination with ceftaroline or ceftazidime against β-lactamase-producing *Enterobacteriaceae* studied in an *in vitro* model of infection. J Antimicrob Chemother 72:762–769. https://doi.org/10.1093/jac/dkw480.
52. Das S, Riccobene T, Carrothers T, Wright J, Macpherson M, Lovern M, Hing J, Xiong Y, Taylor A, Comisar C. 2017. Pharmacokinetic/pharmacodynamic validation of the ceftazidime-avibactam dose in patients with nosocomial pneumonia, including ventilator-associated pneumonia, poster P1185. 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna, Austria, 22 to 25 April 2017.
53. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, Llorens L, Newell P, Pachl J. 2016. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis 62:1380–1389. https://doi.org/10.1093/cid/ciw133.
54. Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, Gasink LB. 2016. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. Lancet Infect Dis 16:661–673. https://doi.org/10.1016/S1473-3099(16)30004-4.
55. Wagenlehner FM, Sobel JD, Newell P, Armstrong J, Huang X, Stone GG, Yates K, Gasink LB. 2016. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. Clin Infect Dis 63:754–762. https://doi.org/10.1093/cid/ciw378.
56. Qin X, Tran BG, Kim M, Wang L, Nguyen D, Chen Q, Song J, Laud PJ, Stone GG, Chow JW. 2017. A randomized, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia. Int J Antimicrob Agents 49:579–588. https://doi.org/10.1016/j.ijantimicag.2017.01.010.
57. Torres A, Zhong N, Pachl J, Timsit JF, Kollef M, Chen Z, Song J, Taylor D, Laud PJ, Stone GG, Chow JW. 2018. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis 18:285–295. https://doi.org/10.1016/S1473-3099(17)30747-8.
58. Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A, Pandey R, Doi Y, Kreiswirth BN, Nguyen MH, Clancy CJ. 2017. Emergence of ceftazidime-avibactam resistance due to plasmid-borne blaKPC-3 mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* infections. Antimicrob Agents Chemother 61:e02097-16. https://doi.org/10.1128/AAC.02097-16.
59. Clinical and Laboratory Standards Institute. 2013. Performance standards for antimicrobial susceptibility testing; 23rd informational supplement. CLSI document M100-S23. Clinical and Laboratory Standards Institute, Wayne, PA.