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Title: **Efficacy of Ceftazidime-Avibactam in a Rat Intra-Abdominal Abscess Model against a Ceftazidime- and Meropenem-Resistant Isolate of Klebsiella pneumoniae Carrying bla$_{KPC-2}$.**

Running Title: Ceftazidime-avibactam vs KPC K. pneumoniae in intra-abdominal abscesses

Authors: Undisclosed for review

Key words: ceftazidime-avibactam; abscess infection; KPC; Klebsiella pneumoniae; rat pharmacokinetics

Abstract (79 words; guideline 150)

Efficacies of ceftazidime-avibactam (4:1 w/w) and ceftazidime were tested against ceftazidime-susceptible (bla_{KPC-2}-negative), and meropenem- and ceftazidime-resistant (bla_{KPC-2}-positive), Klebsiella pneumoniae in a 52-hour, multiple-dose, abdominal abscess model in the rat. Efficacies corresponded to minimum inhibitory concentrations (MICs) measured in vitro and were consistent with drug exposures modelled from pharmacokinetics in infected animals. The ceftazidime, ceftazidime-avibactam, and meropenem control treatments were effective in the rat abscess model against the susceptible strain, whereas only ceftazidime-avibactam was effective against K. pneumoniae harboring bla_{KPC-2}.

Text (2441 words not including Abstract, References, Acknowledgement, Geographic location, Declaration of Interest, or Tables and Figures: guideline maximum 9000)

Introduction

Avibactam is a new inhibitor of serine β-lactamases that is approved in the USA (1) and Europe (2) for therapeutic use in combination with ceftazidime. Avibactam displays a broader spectrum of inhibition than the previously approved β-lactamase inhibitors, clavulanic acid, sulbactam, and tazobactam: a key property being its inhibition of Klebsiella pneumoniae carbapenemase (KPC) variant β-lactamases (3–7). This inhibition translated to efficacy against KPC-producing K. pneumoniae in acute lethal septicemia and neutropenic mouse thigh and intraperitoneal infection models (8, 9). One of the target indications for ceftazidime-avibactam is complicated

intra-abdominal infection (1, 2, 10), which can include intraperitoneal abscesses (11). Therefore, we have examined the efficacy of ceftazidime-avibactam against K. pneumoniae, with or without bla_{KPC-2}, in fecal pellets implanted in the rat abdomen as a model of carbapenem-resistant intra-abdominal abscess infection.

Some of the results of this study have been presented in conference form (Sleger T, Krause KM, Slee AM, Nichols WW. Efficacy of ceftazidime-avibactam in the rat intra-abdominal abscess model against a meropenem-resistant isolate of Klebsiella pneumoniae carrying bla_{KPC-2}. [#B-070], Interscience Conference of Antimicrobial Agents and Chemotherapy San Diego, USA. September 17–21, 2015.).

Methods

Two bacterial strains were used in the efficacy studies: ceftazidime- and meropenem-susceptible K. pneumoniae KB KPC-6 (bla_{KPC-2}-negative) and ceftazidime- and meropenem-resistant K. pneumoniae 283KB7 (bla_{KPC-2}-positive), both from the culture collection of Cerexa Inc (Oakland, USA). Carriage or non-carriage of bla_{KPC-2} was determined by use of Check-Points microarray kits (Check-Points Health BV, Wageningen, The Netherlands) as described previously (12). Carriage of extended spectrum β-lactamase genes was not noted in either strain. Minimum inhibitory concentrations (MICs) were determined by broth microdilution with the concentration of avibactam fixed at 4 mg/L while the concentration of ceftazidime was varied in two-fold increments (13, 14).

Infection and dose-response experiments were performed at ViviSource (now Avastus), Cambridge, MA, USA, under the standards set by its Institution Animal Care and Use Committee (IACUC), consistent with those of the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health, USA. Anesthesia was achieved in animals by oral dosing with Tramadol (4 mg/kg) prior to surgery, and again 24 h after completing surgery. For the abdominal abscess model, bacteria were mixed with sterilized rat feces and molten agar to form plugs of approximate volume 0.5 mL that were surgically implanted (1 per animal; approximately 1 x 10^5 colony-forming units [CFU]/plug) under anesthesia into the abdominal cavities of male Sprague-Dawley rats that weighed 180–225 g. In untreated animals, over the course of 52 h, the plugs developed into distinct, yellow-white encapsulated structures that could be removed intact for analysis. In animals that underwent effective treatment, those abscess-like structures were absent, leaving smaller lesions that could still be dissected out and processed. Each rat was treated at 4, 12, 20, 28, and 36 h after bacterial challenge with one of a range of doses of ceftazidime (8, 16, 32, or 64 mg/kg subcutaneous, sc), ceftazidime-avibactam (8:2, 16:4, 32:8, or 64:16 mg/kg, i.e. 4:1 w/w, sc), or meropenem (40 mg/kg intravenous, iv) as control for expression of carbapenem-resistance in vivo. The specified dose was identical at each time point. The dose regimens were intended to elicit a measurable range of bacterial responses, not to mimic human exposures. The group size for each dose regimen was 10 animals. At 52 h post-challenge, animals were euthanized, abscesses removed and weighed, and viable bacteria counted by homogenization, serial dilution, and plating on tryptic soy agar.

Bacterial count data were summarized graphically using box-and-whisker plots, displaying the median and inter-quartile range of the counts for each dose group. Whiskers contained all data

points that fell within 1.5 times the interquartile range above and below the upper and lower quartile, respectively, with any outliers falling outside that range shown as individual points. No subculturing to test for the possible development of resistance was performed.

Pharmacokinetics (PK) of ceftazidime and avibactam were measured via single sc doses of ceftazidime-avibactam of, respectively, 8 + 2 or 64 + 16 mg/kg (based on weight of parent drug) in groups of four satellite animals subjected to agar plug infections as above with K. pneumoniae 27-908M (bla_{TEM-1}, bla_{SHV-27}, bla_{KPC-2}) using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method (15). Preparation of satellite infected rats and dosing and sampling were performed at NeoSome Life Sciences, Lexington, MA, USA, to OLAW standards under the company's IACUC policies and guidelines. For implanting inoculated agar plugs, rats were anesthetized to surgical depth by isoflurane inhalation confirmed by toe-pinch. A single dose of each combination was given at 12 h following surgery and implantation. Blood samples (100 µL) were taken from the saphenous vein directly into K_2EDTA collection tubes at times 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 6 h after dosing. A pre-dose sample was also taken. Plasma was separated by centrifugation, decanted and stored at –80°C until assay.

Drug concentrations were determined by liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS), detailed methods for which have been described in a separate validation study (15). Briefly, 50 µL samples of rat plasma plasma were dispensed into 96-well plates followed by 250 µL of protein precipitation solution (100 mM ammonium formate, pH 9.0, and acetonitrile; 5:95 by volume) containing internal standards (NXL-105 for avibactam and

cefdinir for ceftazidime). Plates were vortexed for 2 min and then centrifuged at 2150 × g for 5 min at 14°C. Clear supernatant solutions (225 µL) were transferred to clean plates and dried to completeness under nitrogen. Samples were redissolved in water (100 µL), shaken for 10 min, and then transferred to the autosampler of a Shimadzu liquid chromatography system (Shimadzu Corporation, Japan). Chromatographic separation of ceftazidime, avibactam and their respective internal standards was achieved by injecting samples of 1 µL on an ACE 5 C18-AR (3 µm, 50 × 4.6 mm) column (MAC-MOD Analytical, Chadds Ford, PA, USA) maintained at room temperature. The constitution and periods of application of various mixtures of aqueous formic acid (0.1% v/v) and acetonitrile mobile phases are described in full in (15) so are not repeated here. A post-column infusion flow of methanol (0.8 ml/min) was introduced to increase the electrospray performance. Retention times were as follows: avibactam and NXL105 internal standard, 1.25 and 1.06 min, respectively; ceftazidime and cefdinier internal standard, 1.84 and 1.95 min, respectively. Mass spectrometry was performed using an AB Sciex 6500 Triple quadrupole mass spectrometer (AB Sciex, Foster City, CA, USA) operated in electrospray ionization mode. Data were acquired and analysed using Analyst software (v 1.6.2). As above, the mass spectrometer parameters were described in detail in (15) and so are not repeated here.

Rat plasma protein binding was assumed to be 14% for ceftazidime (16), and 2.1% for avibactam (unpublished report, Novexel). Drug exposures, as % of time that unbound compounds exceeded specified concentrations, were calculated with reference to the 52-h period from the initiation of infection to the time at which abscesses were recovered. This 52-h basis was used because, although the inter-dose periods were regular (8 h), there was a 4-h period before dosing started,

and a post-final-dose period of 16 h before efficacy was assessed. Therefore, exposures could not be expressed as percent values of an inter-dose period.

Results and Discussion

Table 1 displays MICs and the corresponding median log(CFU/g abscess) recovered after treatment with the highest repeat doses of ceftazidime (64 mg/kg) or ceftazidime-avibactam (64:16 mg/kg), or the 40 mg/kg repeat dose of meropenem. The efficacies were consistent with expectations based on MICs. Thus, all three treatments were efficacious against the model abscesses containing the bla_{KPC-2}-negative strain of K. pneumoniae, which was susceptible to ceftazidime, ceftazidime-avibactam and meropenem with MICs 4, 0.12, and 0.06 mg/L respectively (median bacterial recovery from 3.3–3.9 logCFU/g abscess: reduced compared with the vehicle control level of 8.8 logCFU/g). However, only the ceftazidime-avibactam treatment was similarly efficacious against the bla_{KPC-2}-containing K. pneumoniae, against which the MIC of ceftazidime-avibactam was 2 mg/L and the median bacterial recovery was near the lower limit of detection at 3.3 logCFU/g. The ceftazidime MIC of >128 mg/L and the meropenem MIC of 32 mg/L against this strain were associated with lack of efficacy against the model abscesses (median bacterial recovery of 9.3 logCFU/g for both treatments). It should be noted that the doses of ceftazidime were identical between ceftazidime monotherapy and ceftazidime-avibactam, with avibactam being dosed at one-quarter that of ceftazidime by weight, as used in other efficacy studies (8, 17) and in the clinical formulation (1, 2). The meropenem treatment served as a control to demonstrate that the possession of bla_{KPC-2} was associated not only with an

elevated MIC of the carbapenem in vitro but that the carbapenem resistance was also expressed in the animal infection model.

Figure 1 provides graphical plots of the bacterial recovery data for all treatments. Results for intra-abdominal abscesses containing the bla_{KPC-2}-negative K. pneumoniae are shown in Figure 1A. As expected, abscesses recovered from rats dosed with vehicle yielded about 10^9 CFU/g abscess (median 8.8 logCFU/g, Table 1). All four ceftazidime-avibactam treatments were fully efficacious, as was the single regimen of meropenem in control animals, with bacterial recoveries near the lower limit of detection (~10^3 CFU/g abscess). The higher doses of ceftazidime of 64 and 32 mg/kg/dose were also efficacious, but efficacy was reduced for the ceftazidime-alone doses of 16 and 8 mg/kg. Growth of the bla_{KPC-2}-positive strain of K. pneumoniae in abscesses in control rats dosed with vehicle also reached about 10^9 CFU/g abscess (median 9.5 logCFU/g, Table 1) over the period of the study (Figure 1B). All the ceftazidime (and the meropenem control) treatments were ineffective against this strain in the model, with bacterial growth being similar to that seen in the abscesses from control animals treated with vehicle (Figure 1B). The effect of meropenem could thus be related qualitatively to the MICs measured in vitro and the result demonstrated that the molecular mechanism of meropenem resistance was expressed in this in vivo infection model. A dose-response relationship was observed for the different ceftazidime-avibactam treatments against the bla_{KPC-2}-positive strain, 283KB7, yielding between 1-log and 6-log reduction in CFU/g abscess compared with abscesses from rats treated with vehicle or ceftazidime monotherapy (Figure 1B).

Based on the above results, the efficacy of ceftazidime-avibactam against K. pneumoniae harboring bla_{KPC-2} demonstrated that distally-dosed avibactam penetrated into the abdominal abscesses and inhibited the β-lactamase there sufficiently for ceftazidime to be bactericidal (12) at that site. This is consistent with the efficacy of ceftazidime-avibactam in complicated intra-abdominal infections (cIAI) that has been reported from phase 2 and phase 3 clinical trials, although noting that organisms harboring bla_{KPC} were not reported from the great majority of patients in those trials (10, 18–20).

As stated in the Methods, the range of ceftazidime and ceftazidime-avibactam doses was chosen to elicit efficacy responses that would demonstrate the effect of avibactam in reversing bla_{KPC-2}-associated ceftazidime-resistance in an in vivo abscess model. The ceftazidime-susceptible isolate was included as control to confirm that in vitro susceptibility to ceftazidime was associated with ceftazidime efficacy in the model. This study was not designed to elucidate the pharmacodynamics of the ceftazidime-avibactam combination. However such pharmacodynamic studies have been performed; and the results were consistent with the antibacterial effect of ceftazidime-avibactam being related to the times that ceftazidime and avibactam exceeded critical concentrations (21, 22). From this time-dependency, one would predict that more frequent dosing would have resulted in greater efficacy of the lower doses of ceftazidime-avibactam against the K. pneumoniae strain harbouring KPC-2 in the current abdominal abscess model. Although this frequency-of-dosing prediction was not tested, the ceftazidime and avibactam exposures, measured as times above their respective critical concentrations, were consistent with the observed efficacies, as follows.

The efficacies of ceftazidime and ceftazidime-avibactam described here were compared with predicted drug exposures calculated from PK models derived from plasma concentration–time courses determined in satellite infected rats. The derived parameters used for the model-based calculations are provided in Table 2. The index of exposure related to the efficacy of ceftazidime is %fT>MIC (2123) which is the percent of time that the ceftazidime concentration in plasma exceeds the MIC measured against the infecting bacterium in vitro. The index that has been used to relate avibactam exposure to restoration of the antibacterial activity of ceftazidime has been time above a threshold concentration: %fT>C_T (21, 22, –24). Threshold concentrations of 0.5 and 1 mg/L have been identified as useful measures for relating avibactam exposures to restoration of ceftazidime activity and were therefore also modeled here. Table 3 shows the modeled free plasma exposures as percentages of the time of duration of the infection.

With respect to the bla$_{KPC-2}$-negative K. pneumoniae KB KPC-6, ceftazidime alone was fully efficacious at 64 and 32 mg/kg (Table 1, Figure 1), which corresponded with calculated fT>MIC 4 mg/L of 42.8% and 35.3% (Table 3). The two lower doses of ceftazidime alone yielded intermediate efficacies (Figure 1) and corresponded to lower calculated fT>MIC 4 mg/L of 27.9% and 20.2%. The in vitro MIC of ceftazidime with avibactam against this bla$_{KPC-2}$-negative strain was lower, being 0.12 mg/L. As a result, when ceftazidime was combined with avibactam (4:1 w/w), the lower doses of 16 and 8 mg/kg were also fully efficacious in that bacterial counts in the abscesses were reduced to near the limit of detection (Figure 1). These lower ceftazidime doses corresponded to values of fT>MIC 0.12 mg/L calculated from the PK model of 65.2% and 58.0% (Table 3). Clearly, the increased potency of ceftazidime in the presence of avibactam against this strain (measured as a decrease in the in vitro MIC on the addition of avibactam)

translated to an increased efficacy of the 16 and 8 mg/kg doses in vivo (Figure 1). The corresponding modeled exposures of avibactam were 11.5% and 8.3% fT>0.5 mg/L (5.4% and 0% fT>1 mg/L) (Table 3).

In the case of the bla_{KPC-2}-positive K. pneumoniae, lack of efficacy at all ceftazidime doses (Figure 1) corresponded to calculated 0% fT>MIC of >128 mg/L (Table 3). In contrast, with co-administered avibactam at 16 mg/kg/dose, which yielded a calculated fT>0.5 mg/L of 24.0% (18.8% fT>1 mg/L), the 64 mg/kg dose of ceftazidime, calculated to yield 50.2% fT>MIC 2 mg/L (i.e. the MIC of ceftazidime-avibactam), corresponded with maximum efficacy (Table 3, Figure 1). Intermediate efficacies against the bla_{KPC-2}-positive strain corresponded to calculated ceftazidime exposures of 42.8, 35.3, and 27.9% fT>MIC of 2 mg/L combined with respective calculated avibactam exposures of 15.4, 11.5, and 8.3% fT> C_T 0.5 mg/L (10.1, 5.4, and 0% fT>C_T 1 mg/L) (Table 3).

The above modelled drug exposures are consistent with efficacy in this abdominal abscess model being achieved at an avibactam exposure somewhat lower than the 50% fT>C_T of 1 mg/L value that has been used as pharmacokinetic/pharmacodynamic (PK/PD) target in dose assessments (~~23~~24). That is, the avibactam PK/PD target used in dose assessments appears to have been conservative relative to the calculated exposure that corresponded to bactericidal efficacy in this rat abscess model against a ceftazidime- and meropenem-resistant isolate of K. pneumoniae harboring bla_{KPC-2}.

Geolocation

The efficacy experiments were performed in Cambridge, MA, USA. Dosing and sampling for measurements of plasma concentrations of ceftazidime and avibactam in satellite infected rats were performed in Lexington, MA, USA. Bioanalysis of blood samples, and PK data analysis and modelling were performed in Waltham, MA, USA. Statistical analyses were performed in Sheffield, UK.

Acknowledgement and Declaration of interest

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279 **References**

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Efficacy of ceftazidime-avibactam in a rat intra-abdominal abscess model against a ceftazidime- and meropenem-resistant isolate of Klebsiella pneumoniae carrying bla_{KPC-2}

Tables and Figures

Table 1. Comparative efficacies of discriminatory doses of ceftazidime, ceftazidime-avibactam, and meropenem against K. pneumoniae KB KPC-6, not carrying, or 283KB7, carrying, bla_{KPC-2} (ceftazidime- and meropenem-susceptible or -resistant, respectively)

Treatment	**Dose (mg/kg/dose)**	**K. pneumoniae (bla_{KPC-2}-negative)**		**K. pneumoniae (bla_{KPC-2}-positive)**	
		MIC (mg/L)	**Median log(CFU/g)[a]**	**MIC (mg/L)**	**Median log(CFU/g)[a]**
Vehicle	-	-	8.8	-	9.5
CAZ [b]	64	4	3.3	>128	9.3
CAZ-AVI [b]	64:16	0.12[c]	3.4	2[c]	3.3
MER [b]	40	0.06	3.9	32	9.3

[a]Limit of detection 3.0 (i.e. 1 x 10^3 CFU/g abscess)

[b]CAZ=ceftazidime; AVI=avibactam; MER=meropenem

[c]Avibactam fixed at 4 mg/L for the MIC measurements

Table 2. Estimated unbound compartmental PK parameters of ceftazidime and avibactam in infected rats

Parameter	**Ceftazidime** [a]	**Avibactam** [b]
No. of compartments	1	2
Absorption rate constant, Ka (h^{-1})	0.90	1.56
Clearance (L/h/kg)	0.33	2.16
Volume (L/kg)	0.079	0.966
$Clearance_2$ (L/h/kg)	-	3.74
$Volume_2$ (L/kg)	-	0.40

[a] Observed unbound non-compartmental parameters: Vz/F (L/kg) = 0.362, Cl/F (L/h/kg) = 0.336 and $t_{½}$ (h) = 0.74

[b] Observed unbound non-compartmental parameters: Vz/F (L/kg) = 2.33, Cl/F (L/h/kg) = 2.16 and $t_{½}$ (h) = 0.73

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393 **Table 3**. Ceftazidime and avibactam exposures calculated from pharmacokinetics in infected rats,
394 expressed as fT>MIC or fT>C_T (threshold concentration) of 0.5 and 1 mg/L

Modeled dose (mg/kg)	**AVI[a] fT>C_T of 0.5 mg/L**	**AVI fT>C_T of 1 mg/L**	**K. pneumoniae (bla_{KPC-2}-negative)**		**K. pneumoniae (bla_{KPC-2}-positive)**	
			MIC (mg/L)	**CAZ[a] fT>MIC [b]**	**MIC (mg/L)**	**CAZ fT>MIC [b]**
CAZ (64)	0.0% [c]	0.0% [c]	4	42.8% [c]	>128 [d]	0.0% [c]
CAZ (32)	0.0%	0.0%	4	35.3%	>128	0.0%
CAZ (16)	0.0%	0.0%	4	27.9%	>128	0.0%
CAZ (8)	0.0%	0.0%	4	20.2%	>128	0.0%
CAZ-AVI (64:16)	24.0%	18.8%	0.12	80.2%	2	50.2%
CAZ-AVI (32:8)	15.4%	10.1%	0.12	72.7%	2	42.8%
CAZ-AVI (16:4)	11.5%	5.4%	0.12	65.2%	2	35.3%
CAZ-AVI	8.3%	0.0%	0.12	58.0%	2	27.9%

(8:2)

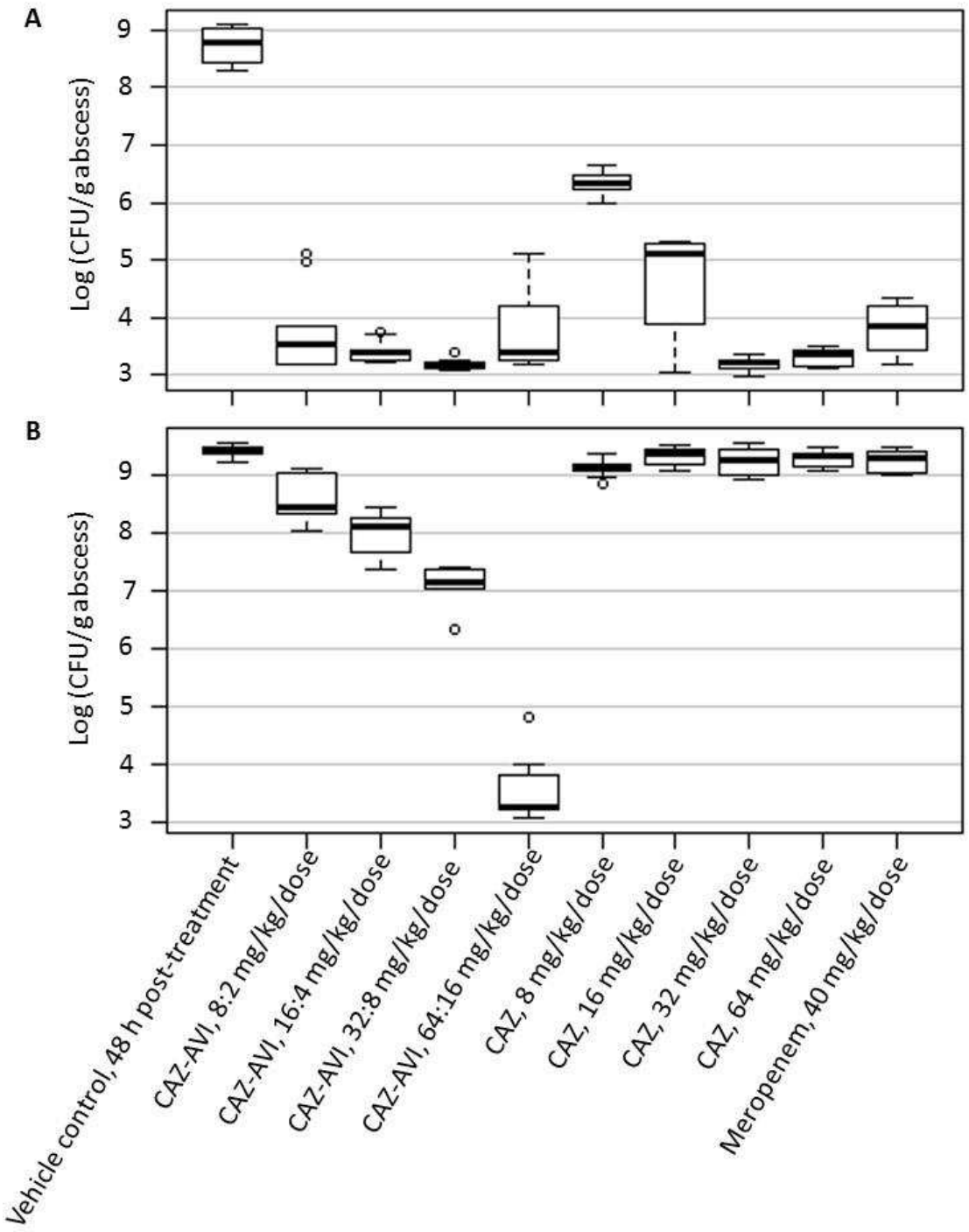
[a] AVI=avibactam; CAZ=ceftazidime

[b] In the case of monotherapy, the ceftazidime fT>MIC was estimated as the time that the free plasma concentration of ceftazidime was ≥ the MIC of ceftazidime. When the therapy was ceftazidime-avibactam, the ceftazidime fT>MIC was estimated as the time that the free plasma concentration of ceftazidime was ≥ the MIC of ceftazidime-avibactam.

[c] Times are expressed as percent of the 52-hour period from the start of the infection to harvesting the abscesses

[d] An MIC value of 256 mg/L was used for calculating ceftazidime fT>MIC of >128 mg/L

FIG 1. Comparative efficacies of ceftazidime, ceftazidime-avibactam, and meropenem against (A) ceftazidime- and meropenem-susceptible, bla_{KPC-2}-negative, K. pneumoniae KB KPC-6, and (B) ceftazidime- and meropenem-resistant, bla_{KPC-2}-positive, K. pneumoniae 283KB7. AVI = avibactam; CAZ = ceftazidime. Magnitudes per dose are shown: see the text for the times of dosing.


A
B
Log (CFU/g abscess)
9
8
7
6
5
4
3
Vehicle control, 48 h post-treatment
CAZ-AVI, 8:2 mg/kg/dose
CAZ-AVI, 16:4 mg/kg/dose
CAZ-AVI, 32:8 mg/kg/dose
CAZ-AVI, 64:16 mg/kg/dose
CAZ, 8 mg/kg/dose
CAZ, 16 mg/kg/dose
CAZ, 32 mg/kg/dose
CAZ, 64 mg/kg/dose
Meropenem, 40 mg/kg/dose

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