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Pharmacodynamic evaluation of tigecycline against *Acinetobacter baumannii* in a murine pneumonia model

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***Objectives*: Tigecycline is an extended-spectrum antibiotic with activity against *Acinetobacter* spp. (ACB), an increasingly common cause of nosocomial pneumonia. Although this compound is under investigation for this indication, supportive pharmacodynamic data are not yet available at this infection site. The objective of this study was to characterize the exposure–response relationship of tigecycline with ACB in an established murine pneumonia model.**

***Methods*: The pharmacokinetic profile of tigecycline was evaluated in infected neutropenic mice. Tigecycline 6.25, 12.5, 25, 50, 100, 200, 300 and 400 mg/kg, in single or two to six divided subcutaneous doses, were tested against all ACB isolates. Efficacy, defined as the $\log_{10}$ change in bacterial cfu/mL, was assessed after a 24 h course of therapy. Tigecycline exposures in serum were corrected for dose-specific protein binding. The relationship between the area under the free concentration–time curve to MIC (*f*AUC/MIC) and change in bacterial density was determined using the sigmoid E_{max} model.**

***Results*: Tigecycline displayed linear pharmacokinetics with a mean half-life of 11.3 ± 1.4 h. Efficacy correlated well with *f*AUC/MIC ($R^2 = 0.96$). The mean 80%, 50% effective and stasis exposures (*f*AUC/MIC) were 17, 8 and 6, respectively. Maximal efficacy for the five *Acinetobacter baumannii* studied was 3.4 log kill.**

***Conclusions*: Tigecycline efficacy in this murine ACB pneumonia model was well predicted by *f*AUC/MIC. Requisite tigecycline exposures for efficacy appear to be higher for ACB pneumonia than for other pathogens reported of non-respiratory infections.**

Keywords: AUC/MIC, *in vivo*, multidrug-resistant, MDR, pharmacokinetics

Introduction

Tigecycline (Tygacil®) has broad Gram-positive and Gram-negative activity, which includes prevalent nosocomial pathogens.[1] While tigecycline is approved by the US Food and Drug Administration for treatment of complicated intra-abdominal infections (cIAIs) and complicated skin and skin structure infections (cSSSIs), another important site to consider from an antibiotic resistance standpoint, and an area of ongoing clinical trials, is nosocomial respiratory tract infections. Tigecycline's ability to escape resistance mechanisms typical of tetracyclines provides an opportunity for its use in nosocomial infections where resistance is more likely, particularly as the incidence of multidrug-resistant (MDR) *Acinetobacter* spp. is rising.[2] *In vitro* data from several studies show that tigecycline has potency against resistant strains of *Acinetobacter* spp. The MIC_{90} of tigecycline against *Acinetobacter* spp. from many areas of the world (Asia, Australia, Europe, North and South America) is 0.5 mg/L,[3,4] while these organisms displayed resistance to all other available antibiotics, including imipenem and meropenem (24.5% and 27.3% resistant, respectively). Given these *in vitro* data, it seems reasonable to investigate the *in vivo* efficacy of tigecycline for the treatment of pneumonia caused by *Acinetobacter* spp. Through the use of the murine pneumonia model, we aimed to explore the antibacterial effects of tigecycline in treating pneumonia caused by *Acinetobacter* spp. while attempting to identify a pharmacodynamic (PD) target for efficacy.

Materials and methods

Antimicrobial test agents

Standard analytical grade tigecycline (Wyeth, Madison, NJ, USA; lot RB5603 exp. 10/08) was used for all *in vitro* and *in vivo* experiments. For all animal studies, the tigecycline powder was weighed and reconstituted with normal saline to achieve desired

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concentrations immediately prior to each experiment. The solution was used within 30 min of reconstitution.

Microorganisms

Six clinical isolates of *Acinetobacter* spp. (five *Acinetobacter baumannii* and one *Acinetobacter lwoffii*) were used in the study. The MIC of tigecycline was determined in triplicate for all organisms by the microdilution method according to CLSI guidelines.[5] The modal MIC was utilized in all PD assessments.

Lung infection (pneumonia) model

Specific-pathogen-free, female CD-1 (ICR) mice weighing ~18–22 g were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN, USA) and utilized throughout these experiments. This study was reviewed and approved by 'The Hartford Hospital Institutional Animal Care and Use Committee'. The animals were maintained and used in accordance with National Research Council recommendations, and provided food and water *ad libitum*. Mice were rendered transiently neutropenic by intraperitoneal injections of cyclophosphamide at 250 and 100 mg/kg of body weight at 4 and 1 day prior to inoculation, respectively.

Acinetobacter spp. isolates were frozen at −80°C in skimmed milk and subcultured twice onto appropriate agar media. For inoculation, a suspension of the test organism was prepared from a second subculture that had been incubated at 37°C for 20–24 h and was adjusted to a turbidity equivalent to that of a 1 McFarland standard in a 3% mucin solution (3.0×10^8 cfu/mL). The bacterial density of the final inoculum was confirmed by serial dilution and culture of an aliquot from each inoculum. The animals were lightly anaesthetized, and pneumonia was induced by instilling 0.05 mL of the bacterial suspension into the mouth of the mice and by completely blocking the nasal cavity of the animal, thus resulting in bacterial inhalation through the mouth to the lungs.

Pharmacokinetic studies

The animals were prepared as described in the pneumonia model section. Four infected groups of 48 CD-1 mice (six mice per timepoint; eight sampling times) were dosed with a single 0.2 mL subcutaneous dose of 6.25, 12.5, 25 or 50 mg/kg tigecycline. Animals were euthanized by CO_2 exposure followed by cervical dislocation prior to sample collection. Blood was obtained from each group of six mice at 0.25, 0.5, 1, 1.5, 2, 4, 6 and 8 h after drug administration, then centrifuged to acquire serum. All serum was stored in polypropylene tubes at −80°C until analysis. Tigecycline concentration was determined using a validated HPLC assay at the Center for Anti-Infective Research and Development, Hartford Hospital; inter-day and intra-day coefficients of variation were <5%.

Protein-binding studies

Protein-binding studies were conducted with a minimum of three independent tests using Amicon Centrifree® Micropartition devices (Millipore, Bedford, MA, USA) with 30000 molecular weight cut-off filters according to the manufacturer's package insert. An aqueous stock solution of the compound containing 1 mg/mL tigecycline was prepared in normal saline. The dilutions were made in freshly collected mouse serum to yield final concentrations of 0.75, 1.5, 6, 12 and 25 mg/L. These concentrations were selected such that the range incorporated the peak serum concentration profile of the doses to be utilized in the PD studies. Each of the serum solutions was heated at 37°C in a shaking water bath for 10 min. Exactly 0.9 mL of each serum solution was transferred into three ultrafiltration devices and centrifuged for 25 min at 10°C at 1000 **g** to generate an ultrafiltrate volume of ~250 μL. In addition, non-specific protein binding of the drug to the filter device was assessed, and the compound was not bound to the filter apparatus.

Percentage protein binding (%PB) at each prepared concentration was calculated using the following equation: $\%PB=[(S-SUF)/S]\times100$, where S is the tigecycline concentration in the initial serum solutions and SUF is the tigecycline concentration in the ultrafiltrate.

'Therapeutic efficacy of tigecycline' as defined by bacterial density

To assess the *in vivo* bactericidal activity of tigecycline against the *Acinetobacter* isolates, treatment was initiated 4 h after inoculation. Mice were given tigecycline at doses of 6.25 (single dose), 12.5 (single dose), 25 (single dose), 50 (single dose), 100 (50 mg every 12 h), 200 (50 mg every 6 h), 300 (50 mg every 4 h) and 400 (50 mg every 3 h) mg/day. All doses were given subcutaneously. Control animals received sterile normal saline in the same volume (0.2 mL) and schedule as the most frequent active drug regimen. Untreated control animals (six per group) were sacrificed just prior to antibiotic initiation (0 h) and after 24 h, along with all drug-treated animal groups at the 24 h timepoint. After the animals were sacrificed (euthanasia by CO_2 exposure followed by cervical dislocation), all lobes of the lung were removed and homogenized in normal saline. Serial dilutions of the homogenate were plated onto blood agar for cfu determination. For the purposes of these studies, efficacy (change in bacterial density) was calculated as the change in bacterial cfu/mL obtained in treated mice after 24 h compared with the cfu in the 0 h control animals.

PD analysis

A dose–response curve was constructed by plotting the change in $\log_{10}$ cfu/mL versus the area under the free concentration–time curve to MIC (*f*AUC/MIC) (using the sigmoid E_{max} model) for each *Acinetobacter* isolate to determine the effective exposure indexes [EIs, i.e. EI_{80} (exposure values required to produce 80% of maximal effect), EI_{50} (exposure values required to produce 50% of maximal effect) and stasis]. Only the *f*AUC/MIC was assessed in this study as this PD parameter has been previously determined to be the most closely correlated to efficacy in other *in vivo* studies conducted in our laboratory.[6,7]

Results

The genotypic identification and phenotypic profile of the *Acinetobacter* isolates are displayed in Table 1. The tigecycline MICs for the *Acinetobacter* isolates ranged from 0.25 to 1 mg/L. One of the six isolates was identified as an *A. lwoffii* with an MIC of tigecycline of 0.25 mg/L and susceptibility to all antibiotics tested.

The serum pharmacokinetic parameters are summarized in Table 2. The range of the AUC_{0-24} (mg·h/L) was 10.4–103.5 with the dosage regimens used. Figure 1 displays total serum concentrations of tigecycline after various single subcutaneous doses.

The mean starting (0 h) bacterial density in the lungs of the control mice was 3.47×10^7 cfu/mL. Twenty-four hours after

Table 1. *Acinetobacter* spp. (ACB) and antimicrobial susceptibility[a]

Antibiotics	MIC (mg/L) and interpretation											
	ACB 25-49 *A. baumannii*		ACB 5-11 *A. baumannii*		ACB 8-4 *A. baumannii*		ACB 25-14 *A. baumannii*		ACB 5-19 *A. lwoffii*		ACB 25-15 *A. baumannii*	
ETP[b]	8		4		2		2		2		128	
MEM	2	(S)	0.5	(S)	0.5	(S)	1	(S)	0.125	(S)	64	(R)
IPM	0.125	(S)	0.25	(S)	0.25	(S)	0.25	(S)	0.25	(S)	>64	(R)
CIP	0.5	(S)	0.5	(S)	0.5	(S)	0.125	(S)	0.125	(S)	>64	(R)
LVX	0.125	(S)	0.125	(S)	0.25	(S)	0.125	(S)	0.125	(S)	16	(R)
MXF	0.125	(S)	0.064	(S)	0.125	(S)	0.064	(S)	0.064	(S)	8	(R)
AMK	2	(S)	2	(S)	2	(S)	2	(S)	1	(S)	32	(I)
GEN	1.5	(S)	1	(S)	1	(S)	2	(S)	0.5	(S)	64	(R)
TOB	1	(S)	0.5	(S)	0.5	(S)	0.5	(S)	0.5	(S)	64	(R)
SAM	4	(S)	2	(S)	2	(S)	2	(S)	2	(S)	64	(R)
ATM[b]	64		32		16		32		16		64	
TZP	32	(I)	16	(S)	4	(S)	2	(S)	0.25	(S)	>512	(R)
CRO	32	(R)	16	(I)	16	(I)	16	(I)	4	(S)	24	(R)
FEP	4	(S)	4	(S)	2	(S)	2	(S)	0.25	(S)	64	(R)
CAZ	8	(S)	8	(S)	4	(S)	4	(S)	1	(S)	64	(R)
TGC[b]	0.5		0.5		1		0.25		0.25		0.5	

ETP, ertapenem; MEM, meropenem; IPM, imipenem; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; SAM, ampicillin/sulbactam; ATM, aztreonam; TZP, piperacillin/tazobactam; CRO, ceftriaxone; FEP, cefepime; CAZ, ceftazidime; TGC, tigecycline.

[a]Antimicrobial susceptibility presented as MIC (mg/L) and interpretation; S = susceptible, I = intermediately susceptible and R = resistant.

[b]No official MIC breakpoint interpretation.

Table 2. Pharmacokinetic parameters of tigecycline after a single subcutaneous dose in a pneumonia murine model infected by *A. baumannii*

Dosing regimen (mg/kg)	C_{max} (mg/L)	T_{max} (h)	AUC_{0-24} (mg·h/L)	Half-life (h)	V (L/kg)	Protein binding (%)
6.25	1.17	0.40	10.40	9.80	4.63	74.2
12.5	2.73	0.59	23.28	11.36	3.15	87.9
25	4.77	1.02	57.24	12.33	2.38	91.2
50	10.19	1.06	103.48	11.55	2.44	92.9

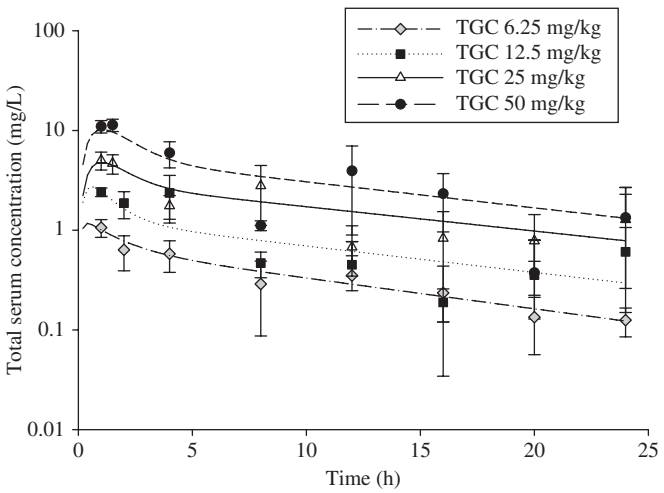

Figure 1. Total concentrations of tigecycline (TGC) after various single subcutaneous doses.

inoculation, the bacterial density had increased by 1.37 $\log_{10}$ cfu on average (range 0.68–2.4).

In this murine pneumonia model, tigecycline displayed bactericidal activity (i.e. >3 log kill) in four of the five *A. baumannii* isolates tested. Similar bactericidal activity was also seen in the *A. lwoffii* isolate. The observed mean maximal cfu reductions in tigecycline-treated animals after 24 h of exposure were 3.47 $\log_{10}$ cfu (range 2.63–4.38) and were very similar to the values defined by the fitted data (Table 3).

The relationship between the antimicrobial activities of tigecycline and the *f*AUC/MIC was assessed for each individual *A. baumannii* isolate. The mean correlation coefficient (R^2) of the fitted curves was 0.964 [range 0.929–0.999 (Table 3)].

Table 3 also displays the individually generated EI_{80}, EI_{50} and stasis exposure values for the five *A. baumannii* isolates studied. The mean value from the individual modelling of effects was very similar to that defined in the composite curve (Figure 2; EI_{80}, EI_{50} and stasis values were 17.16, 8.21 and 5.92, respectively, and the R^2 was 0.7278). From the composite curve, the predicted *f*AUC/MIC required for 1, 2, and 3 log kill are 2.17, 8.78 and 26.49, respectively.

As displayed in Figure 3, the PD profile of tigecycline against the *A. lwoffii* appeared substantially enhanced versus that of the *A. baumannii* with the same MIC.

Table 3. *f*AUC/MIC values for corresponding effective EI of tigecycline against five *A. baumannii* isolates in an immunocompromised murine (ICR) pneumonia model

A. baumannii	Correlation coefficient (R^2)	*f*AUC/MIC			Maximum $\log_{10}$ cfu reduction (cfu/mL)
		EI_{80}	EI_{50}	stasis	
ACB 25-14	0.999	18.18	11.06	8.04	−3.35
ACB 25-15	0.904	30.40	11.23	7.23	−3.31
ACB 5-11	0.965	10.06	4.46	1.48	−4.33
ACB 25-49	0.974	15.37	8.73	8.59	−2.16
ACB 8-4	0.979	11.80	5.58	4.24	−3.88
Mean	0.964	17.16	8.21	5.92	−3.41
SD	0.035	8.04	3.10	2.99	0.81

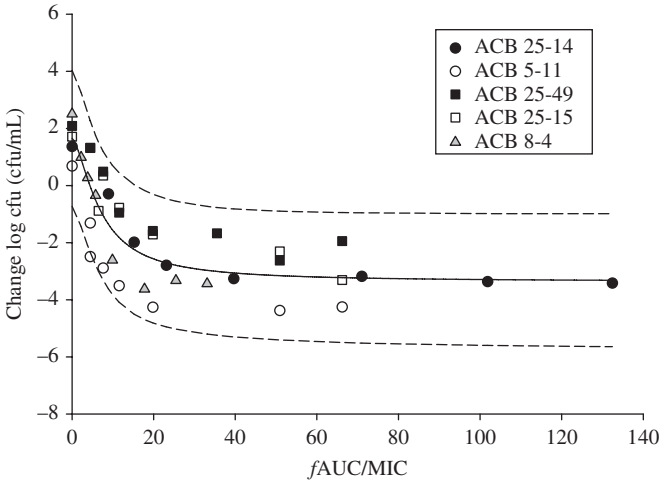

Figure 2. Composite assessment of tigecycline's antibacterial effect versus *f*AUC/MIC (mean ± 95% confidence interval) for five *A. baumannii*.

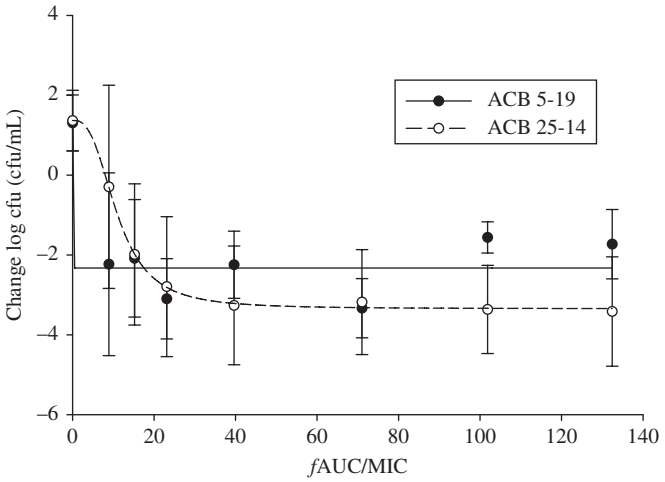

Figure 3. Antimicrobial activity of tigecycline versus *f*AUC/MIC against *Acinetobacter* isolates with MICs of tigecycline of 0.25 mg/L.

Discussion

Tigecycline, a novel antimicrobial agent, has a broad-spectrum activity against many organisms and penetrates into lung tissue,[8] thus this compound may be a viable treatment option for non-pseudomonal pneumonias. Moreover, tigecycline displays *in vitro* activity against *A. baumannii*, including MDR strains that may be identified in difficult-to-treat nosocomial pneumonias.

Good clinical and microbiological efficacies have been reported when using tigecycline in patients infected by MDR *Acinetobacter* spp. infections other than cSSSIs and cIAIs.[9–12] An open-label, Phase 3, non-comparative, multicentre study assessed the efficacy and safety of intravenous tigecycline in hospitalized patients with serious infections caused by Gram-negative organisms.[10] In that study, *A. baumannii* was the most frequently isolated organism from cSSSIs, cIAIs, community-acquired pneumonia and hospital-acquired pneumonia (HAP). The clinical cure and microbiological eradication rate at the test of cure for HAP caused by *A. baumannii* were 75% and 46%, respectively. Additionally, other authors have reported the clinical efficacy of tigecycline against *A. baumannii* causing pneumonia; however, the non-comparative nature of these data requires confirmation.[9,11] While well-controlled clinical data are required to fully assess the viability of tigecycline as a therapeutic modality for pneumonia, Conte *et al.*[8] reported that the C_{max}/MIC_{90}, AUC/MIC_{90}, $time/MIC_{90}$ and extended serum and intrapulmonary half-lives of this compound were favourable for the treatment of tigecycline-susceptible respiratory pathogens.

In an effort to gain insights into the clinical utility of novel compounds, animal models of infection are often used as a bridging tool. The efficacy of tigecycline in immunosuppressed experimental murine pneumonia due to *A. baumannii* has recently been reported by Song *et al.*[13] While these authors reported the lack of efficacy of tigecycline monotherapy, pharmacokinetic exposures were not determined, thus PD profiling was not undertaken.

Our current study aimed to define both the magnitude of the *in vivo* antibacterial effects as well as the exposures required (i.e. *f*AUC/MIC) to produce these reductions in bacterial load. We utilized the PD parameter of *f*AUC/MIC to assess efficacy because this parameter has been correlated to outcome in both murine models of infection and man.[6–7,14–16]

Our study noted the *in vivo* bactericidal activity of tigecycline against various *A. baumannii* (MIC 0.25–1.0 mg/L) causing pneumonia in this murine model. These studies also revealed that *f*AUC/MIC exposures of 2.17 and 8.78 were required to produce 1 and 2 log kill, respectively. In addition, another index

for the comparative assessment of antibacterial efficacy is the effective exposure value [i.e. EI_{80} (exposure value required to produce 80% of maximal effect) or EI_{50} (exposure value required to produce 50% of maximal effect)]. The mean EI_{80} and EI_{50} of tigecycline against *A. baumannii* were 17.2 and 8.2, respectively, in this current study. In comparison, the required mean EI_{80} and EI_{50} exposures for Enterobacteriaceae using the murine thigh model were 7.3 and 4.5, respectively.[6] While the thigh model routinely requires a slightly lower drug exposure to get similar bacterial reductions to that of the pneumonia model, our data suggest that considerably more drug exposure is required to produce these antibacterial effects in *Acinetobacter* when compared with that in Enterobacteriaceae. Although the MDR isolate (ACB 25-15) appears to require substantially more exposure (ED_{80}) than the other isolates, its ED_{50} and static exposures are quite similar to those of the other isolates. While the ED_{80} suggests the need for higher exposures, it is likely that this is an artefact due to the distribution of the available data points used in the mathematical derivation of this value. As such, additional MDR isolates are required to confirm whether increased exposures are actually required for organisms possessing this phenotypic profile. Unfortunately, while PD targets have been reported in man for the Enterobacteriaceae causing cIAIs, no such data are available for *A. baumannii*.[15] The efficacy of tigecycline against MDR *A. baumannii* causing ventilator-associated pneumonia (VAP) was reported as a retrospective case series.[9] Twenty-five patients with VAP and/or bacteraemia received tigecycline (five patients had monotherapy while the others received combination therapy). Monotherapy resulted in 100% clinical resolution and 100% microbiological eradication (3/3 patients with repeat cultures). Due to the frequent use of combination therapy and the lack of pharmacokinetic data, a PD index could not be identified in this patient population. Another study reporting the efficacy of tigecycline against *A. baumannii* infections (five VAP, one tracheobronchitis, one mediastinitis, one urinary tract infection, one cellulitis and one diabetic ulcer with osteomyelitis) demonstrated that 80% (4/5) of patients infected with intermediately susceptible (MIC >2 or <8 mg/L) organisms died, whereas no patient (0/4) infected with susceptible isolates (MIC ≤ 2 mg/L) died.[17] Thus the optimal *in vivo* exposures required for this pathogen remain elusive in man.

While we have defined the serum exposure (*f*AUC/MIC) that is required for efficacy in this murine pneumonia model, direct application of this PD profile to human infection is made difficult by the following: (i) the tigecycline concentration–time profile in the lung may be different between mouse and man; and (ii) all animals were made profoundly neutropenic, a situation that is not routine in the clinically infected patient with pneumonia. Given these confounding issues, extrapolation of our current dataset to man using the murine efficacy target defined by a 1–2 log cfu reduction (i.e. *f*AUC/MIC 2.17–8.78) in the context of the available pharmacokinetic data from infected humans (AUC 6.37 mg·h/L)[18] with protein binding (79%) correction[16] suggests that tigecycline doses of up to 200 mg/day may be required to provide adequate exposure for *A. baumannii*.

We also observed a different PD profile for the *A. lwoffii* isolate. *A. lwoffii* is not a common cause of either HAP or VAP; however, this organism has been reported as a cause of other infections.[19–21] As a result of our observed difference in the kill profile of the single *A. lwoffii* isolate, these data were not incorporated into the composite analyses with the *A. baumannii*. While this profound killing profile was noted in only a single *A. lwoffii*, these data suggest that additional assessments against this species may provide greater insight into the antibacterial effects of tigecycline against *Acinetobacter*.

In summary, for *A. baumannii*, which is a common cause of HAP or VAP, our data revealed the bactericidal activity of tigecycline against this pathogen. Moreover, the *in vivo* PD parameter of *f*AUC/MIC was well correlated with antibacterial efficacy. While several reports have demonstrated the clinical and microbiological efficacy of tigecycline for nosocomial pneumonia due to *A. baumannii*, additional comparative studies are required as is the determination of the compound's PD profile in man.

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Transparency declarations

None to declare.

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