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In vitro activity of tigecycline against colistin-resistant *Acinetobacter* spp. isolates from Korea

Sir,

Acinetobacter spp. has increasingly been recognised as an important nosocomial pathogen. However, antimicrobial treatment of *Acinetobacter* infections has become a challenge due to the emergence of multidrug-resistant (MDR) and pandrug-resistant (PDR) isolates. Although colistin fell into disuse by the 1980s because of its nephrotoxicity and neurotoxicity, it has again been brought into clinical use due to the emergence of MDR Gram-negative bacilli, including *Acinetobacter*. Since its reintroduction, it has been widely used against *Acinetobacter* infections because of the low resistance rate and it is now considered one of the last resorts against MDR or PDR *Acinetobacter* infections [1]. However, high resistance rates to colistin among *Acinetobacter* isolates from Korea have been recently reported by us [2]. The increased incidence of colistin-resistant *Acinetobacter* isolates highlights the urgent need for new antimicrobials. Several studies have reported excellent in vitro activity of tigecycline against *Acinetobacter* spp. isolates, including MDR isolates [3], although one recent study from Israel demonstrated high tigecycline resistance [4]. However, no study has reported on the in vitro activity of tigecycline against colistin-resistant *Acinetobacter* spp. isolates.

To investigate the in vitro activity of tigecycline against colistin-resistant *Acinetobacter* spp. isolates, a total of 145 colistin-resistant *Acinetobacter* spp. isolates were included in this study. All isolates were collected from four Korean hospitals between 2006 and 2007. Species identification was performed using partial *rpoB* gene sequences [2]. Antimicrobial susceptibility testing was performed by broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) [5]. The interpretive criteria used were those of the CLSI [5]. Regarding tigecycline, interpretive criteria were defined based on the US Food and Drug Administration (FDA) breakpoint criteria for Enterobacteriaceae (susceptible $\leq$2 μg/mL, intermediate 4 μg/mL and resistant $\geq$8 μg/mL).

A total of 120 isolates belonged to *Acinetobacter calcoaceticus–A. baumannii* complex (Acb complex), comprising 35 isolates belonging to *A. baumannii* subgroup A (Aba-A, formery *A. baumannii* subgroup I), 42 to *A. baumannii* subgroup B (Aba-B, formerly *A. baumannii* subgroup III), 37 to *Acinetobacter* genomic species 13TU and 6 to *Acinetobacter* genomics species 3. The other 25 isolates belonged to *Acinetobacter baylyi*, *Acinetobacter haemolyticus*, *Acinetobacter junii*, *Acinetobacter parvus* and *Acinetobacter* genomic species (10, 11 and 16, respectively).

Of the 145 colistin-resistant *Acinetobacter* spp. isolates, 24 (16.6%) and 27 (18.6%) isolates were resistant to imipenem and meropenem, respectively. Resistance rates against other antimicrobials were as follows; 20.7% to tetracycline; 22.8% to ciprofloxacin; 11.7% to rifampicin; 29.0% to amikacin; 27.6% to cefepime; 22.1% to ceftriaxone; 25.5% to ceftazidime; 16.6% to piperacillin/tazobactam; 15.2% to ampicillin/sulbactam. In this study, imipenem and meropenem resistance rates among colistin-resistant *Acinetobacter* spp. isolates were higher than those among colistin-susceptible isolates, as determined in our previous study (8.9% and 12.5%, respectively) [2]. Although Li et al. [6] showed that carbapenem susceptibilities increased in induced colistin-resistant *A. baumannii* isolates, our result indicates that carbapenem and colistin resistances can co-occur in many *Acinetobacter* spp. isolates.

In this study, 14 colistin-resistant *Acinetobacter* spp. isolates (9.7%) were non-susceptible to tigecycline. All tigecycline-non-susceptible isolates, except two, belonged to the Acb complex (Table 1). Four colistin-resistant *Acinetobacter* spp. isolates were resistant to tigecycline; two isolates belonged to Aba-A and one isolate each belonged to *Acinetobacter* genomic species 13TU and 11. Whilst the MIC_{90} values (minimum inhibitory concentration for 90% of the organisms) of all *Acinetobacter* spp. isolates was 2 μg/mL, that of the Acb complex, Aba-A and genomic species 13TU isolates was 4 μg/mL. The MIC_{50} (MIC for 50% of the organisms) was higher in Aba-A isolates (1 μg/mL).

Recent in vitro studies showed various tigecycline susceptibilities among MDR *A. baumannii* isolates. Whilst only 3.7% of those isolated in Italy were resistant to tigecycline, 65.9% of those isolated in Israel were resistant [4,7]. Although the high tigecycline resistance rate was based on the Etest method and is now limited in Israel, the emergence of tigecycline-non-susceptible *A. baumannii* bloodstream infections, in addition to high resistance rates, represents a serious challenge to clinicians. Although many in vitro studies have shown good activity of tigecycline against MDR *A. baumannii*, the clinical efficacy of tigecycline is still unproven. In this study, tigecycline was the most active antimicrobial agent tested against colistin-resistant *Acinetobacter* isolates. Fourteen isolates were non-susceptible to tigecycline and only four were resistant. Thus, tigecycline may be one of most useful options for treatment of *Acinetobacter* infections caused by colistin-resistant and imipenem-resistant isolates.

Table 1
In vitro activity of tigecycline against colistin-resistant *Acinetobacter* spp. isolates.

Species or complex	*n* (%)			MIC (mg/L)	
	R	I	S	MIC_{90}	MIC_{50}
Acb complex (*n* = 120)	3 (2.5)	9 (7.5)	108 (90.0)	4	0.5
Aba-A (*n* = 35)	2 (5.7)	4 (11.4)	29 (82.9)	4	1
Aba-B (*n* = 42)	–	1 (2.4)	41 (97.6)	2	0.5
13TU (*n* = 37)	1 (2.7)	4 (10.8)	32 (86.5)	4	0.5
Others (*n* = 25)	1 (4.0)	1 (4.0)	23 (92.0)	1	0.5
Total (*n* = 145)	4 (2.8)	10 (6.9)	131 (90.3)	2	0.5

R, resistant; I, intermediate; S, susceptible; $MIC_{50/90}$, minimum inhibitory concentration for 50% and 90% of the isolates tested, respectively; Acb complex, *Acinetobacter calcoaceticus–A. baumannii* complex; Aba-A, *A. baumannii* subgroup A; Aba-B, *A. baumannii* subgroup B; 13TU, *Acinetobacter* genomic species 13TU.

However, we also found *Acinetobacter* spp. isolates that were non-susceptible to all antimicrobial agents tested. That is, regardless of tigecycline susceptibility, 12 isolates belonging to Aba-A were simultaneously resistant to all antimicrobial agents tested in this study. Of these, three isolates were also non-susceptible to tigecycline. This implies that tigecycline resistance may co-occur with other antimicrobial resistances, which may limit the usefulness of this antibiotic.

In summary, tigecycline showed good in vitro activity against *Acinetobacter* spp. isolates, but some of the isolates were resistant to all antimicrobial agents, including tigecycline. The emergence of *Acinetobacter* spp. isolates resistant to all drugs is worrying due to the lack of antimicrobial options available for treatment of these infections.

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Experience with extended-infusion meropenem in the management of ventilator-associated pneumonia due to multidrug-resistant *Acinetobacter baumannii*

Sir,

We read with interest the Journal's recent review of the available evidence on continuous-infusion β-lactam antibiotic therapy in severe infections [1]. This article concluded that the data suggest that seriously ill patients with severe infections requiring significant antibiotic courses (≥4 days) may achieve better outcomes with continuous-infusion treatment, but did not include any data for carbapenems, one of the most widely used antibiotic classes in this type of sepsis. We therefore wish to add our experience with extended-infusion meropenem to the picture presented in the abovementioned review.

Hospital-acquired pneumonia (HAP) is associated with an attributable mortality between 33% and 50%. In Intensive Care Units (ICUs), increased mortality rates are associated with infection due to multidrug-resistant (MDR) bacteria, especially *Pseudomonas aeruginosa* and *Acinetobacter baumannii* species [2]. These infections in particular therefore demand the greatest confidence in using antibiotics appropriately and in optimising their effects. Whereas the recent review noted that the characteristics of β-lactam antibiotics and the theories of pharmacokinetics and pharmacodynamics mean that continuous infusion of ceftazidime and piperacillin has pharmacodynamic advantages over bolus dosing in seriously ill patients [1], these same features also apply to extended-infusion meropenem.

Meropenem remains active for 4 h in normal saline solution at room temperature [3] and it has previously been shown that the pharmacokinetics of continuous-infusion meropenem favour