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In Vitro Activities of Tigecycline, Minocycline, and Colistin-Tigecycline Combination against Multi- and Pandrug-Resistant Clinical Isolates of *Acinetobacter baumannii* Group▽

Acinetobacter baumannii has emerged worldwide as an important nosocomial and opportunistic pathogen, particularly in intensive care units (7). Treatment is difficult due to the high rate of multidrug resistance (including carbapenems) (4, 7). As a result, polymyxins have been prescribed as the agent of last resort. Nevertheless, overprescription and the lack of an optimal dosing could lead to colistin resistance (3, 5, 9).

Tigecycline has been tested against *Acinetobacter* spp. (4). However, there are scarce data regarding colistin- and pandrug-resistant (PDR) *A. baumannii* clinical isolates (12, 13). We tested tigecycline, minocycline, and tigecycline-colistin combination against *A. baumannii* isolates displaying different antimicrobial profiles, including colistin resistance.

A total of 150 nonduplicate *A. baumannii* clinical isolates were tested, including 89 colistin-susceptible isolates (randomly selected) and 61 colistin-resistant isolates (MICs of 4 to 256 μg/ml). They were collected from our 2,037-bed tertiary care hospital between May 2000 and November 2006 (a period in which tigecycline was not licensed in Spain yet). MicroScan (Dade-Behring) was used for identification and for susceptibility testing to the following antibiotics: ampicillin/sulbactam, piperacillin-tazobactam, aztreonam, ceftriaxone, ceftazidime, cefotaxime, cefepime, imipenem, meropenem, ciprofloxacin, ofloxacin, cotrimoxazole, tetracycline, gentamicin, tobramycin, and amikacin. The colistin-resistant isolates were confirmed as described previously (2). Tigecycline (Wyeth), minocycline, and colistin (Sigma) MICs were measured by the broth microdilution method according to CLSI, using fresh cation-adjusted Müller-Hinton broth (Becton-Dickinson).

The results are presented in Table 1. Overall, tigecycline MICs were three dilutions lower than minocycline MICs. Due to the colistin resistance displayed out of the PDR group, the whole collection was also categorized according to the colistin phenotype. Both the colistin-resistant and -susceptible isolates showed equal tigecycline $MIC_{50/90}$s (1/2 μg/ml, respectively). Although both groups displayed comparable $MIC_{50/90}$s to minocycline (8/16 and 8/8 μg/ml, respectively), the susceptibility rates were 18 and 49.4%, respectively.

Tigecycline and colistin could eventually be prescribed simultaneously. Therefore, we assessed their interactions with the checkerboard assay, using 0.12, 0.25, 0.5, 1, 2, and 4× MIC concentrations and a final inoculum of 5×10^5 CFU/ml. All 35 isolates (selected by colistin MICs of 0.12 to 4 μg/ml) tested displayed indifference, with fractional inhibitory concentration indices ranging from 0.75 to 2. These results agree with those reported using Etest methodology (10) and time-kill studies (11). Although synergy has been described using the checkerboard method when testing colistin- and polymyxin B-tigecycline combinations (8), none of these were confirmed to be synergistic by time-kill kinetics.

Here we report tigecycline MICs against truly PDR *A. baumannii* isolates. Due to the lack of CLSI breakpoints for *Acinetobacter*, no susceptibility rate could be inferred. It should be noted that our MIC_{90} (2 μg/ml), equal to those in most studies (4), is higher than the achievable concentration of tigecycline in serum at normal dosing (0.63 μg/ml) (7). In fact, clinical failures and emergence of resistance have been reported (1, 4, 6). Conversely, tigecycline could provide higher concentration in tissues, implying a theoretical role for tissue-based infections (7). Nevertheless, the only granted use of tigecycline so far is for the treatment of complicated skin/skin structure and intra-abdominal infections caused by bacteria other than *Acinetobacter* (the U.S. Food and Drug Administration).

To date, only the British Society of Antimicrobial Chemotherapy has provided criteria to designate tigecycline-susceptible and -resistant *A. baumannii* isolates (≤1 and >2 μg/ml, respectively). Implementation of these breakpoints would severely limit the use of tigecycline. However, it could effectively be prescribed as salvage therapy for certain types of infections caused by PDR *A. baumannii*.

TABLE 1. Results of in vitro susceptibility testing of 150 *A. baumannii* group clinical isolates

Isolate[a]	*n*	Tigecycline[b]			Minocycline			% Susceptible
		MIC (μg/ml)[c]			MIC (μg/ml)[c]			
		Range	50%	90%	Range	50%	90%	
PDR	46	0.5–8	1	2	0.25–16	8	16	8.7
XDR	40	0.25–4	1	2	0.25–32	8	16	30
IPM-S	64	0.03–2	1	2	≤0.06–16	4	8	60.9
Total	150	0.03–8	1	2	≤0.06–32	8	16	36.6

[a] The isolates were classified according to the susceptibility to the antimicrobials listed in the text (excluding tigecycline and minocycline) as follows: PDR, resistant to all antibiotics including colistin; extensively drug resistant (XDR), only susceptible to colistin; and (for the rest of the isolates), imipenem susceptible (IPM-S), displaying variable susceptibility to the remaining agents.
[b] No susceptibility breakpoint for *Acinetobacter* has been provided by CLSI.
[c] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

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