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In Vitro Activities of Tigecycline against Clinical Isolates of *Aeromonas*, *Vibrio*, and *Salmonella* Species in Taiwan▽

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All 198 *Salmonella* isolates (58.6% of isolates were resistant to tetracycline), 92 *Vibrio* isolates (4.4% of isolates were resistant to tetracycline), and 200 of 201 *Aeromonas* isolates (39.3% of isolates were resistant to tetracycline; 1 *A. caviae* isolate had a tigecycline MIC of 4 μg/ml) in our study were susceptible to tigecycline, by U. S. Food and Drug Administration criteria for *Enterobacteriaceae*.

Salmonella and *Vibrio* species are commonly associated with food-borne disease, bacteremia, peritonitis, and soft tissue infections (4, 6, 9). Wound infection and bacteremia caused by *V. vulnificus* are associated with mortality rates as high as 55% (4, 9). Strains of *Aeromonas* species could also cause fatal soft tissue infection in immunocompromised hosts and especially in cirrhotic patients (10, 11, 14). Traditionally, cefotaxime, ceftriaxone, and fluoroquinolones were active against *V. parahaemolyticus* and *V. vulnificus* infection (14). However, emerging resistance among *Aeromonas* and *Salmonella* species has been reported recently (15).

Tigecycline, a novel glycylcycline antimicrobial agent, has an expanded spectrum of antimicrobial activities against various clinically important pathogens including most members of the family *Enterobacteriaceae* (8, 18). Except for tigecycline activity against *Salmonella* species, the in vitro activities of tigecycline against *Aeromonas* and *Vibrio* species have not been previously reported (16).

A total of 491 nonduplicated (one isolate per patient) isolates were included in the current study (Table 1). These isolates were recovered from various clinical specimens, including blood (58%), stool (17%), wound pus (15%), and abscess fluid (10%). These organisms were identified by conventional methods (8, 10, 13). All of these isolates were collected from patients between January 2001 and December 2006 in National Taiwan University Hospital, a 2,200-bed tertiary referral hospital in northern Taiwan.

Susceptibility test results for cefotaxime and ciprofloxacin were obtained from routine laboratory reports generated by the disk diffusion method according to Clinical and Laboratory

TABLE 1. Distribution of MICs of tigecycline for 491 isolates of *Aeromonas*, *Salmonella*, and *Vibrio* species[a]

Bacteria (no. isolates tested)	No. of isolates susceptible to each indicated MIC (accumulated %)									% of susceptibility (FDA/EUCAST)[b]		
	<0.03	0.06	0.12	0.25	0.5	1	2	4	8	Susceptible	Intermediate	Resistant
Aeromonas spp. (total, 201)												
A. hydrophila (81)	0 (0)	2 (1)	7 (11)	50 (73)	14 (90)	7 (99)	1 (100)	0 (100)	0 (100)	100/98.8	0/1.2	0/0
A. caviae (63)	0 (0)	0 (0)	2 (3)	34 (57)	22 (92)	3 (97)	1 (98)	1 (100)	0 (100)	98.4/96.8	1.6/1.6	0/1.6
A. sobria (57)	0 (0)	0 (0)	16 (28)	28 (77)	11 (96)	2 (100)	0 (100)	0 (100)	0 (100)	100/100	0/0	0/0
Salmonella spp. (total, 198)												
S. serotype Choleraesuis (63)	0 (0)	0 (0)	1 (2)	4 (8)	39 (70)	18 (98)	1 (100)	0 (100)	0 (100)	100/98.4	0/1.6	0/0
S. serotype Typhimurium (63)	0 (0)	0 (0)	0 (0)	29 (46)	30 (94)	3 (98)	1 (100)	0 (100)	0 (100)	100/98.4	0/1.6	0/0
Salmonella serogroup O7 (13)	0 (0)	0 (0)	0 (0)	5 (38)	8 (100)	0 (100)	0 (100)	0 (100)	0 (100)	100/100	0/0	0/0
Salmonella serogroup O8 (14)	0 (0)	0 (0)	0 (0)	7 (50)	7 (60)	0 (100)	0 (100)	0 (100)	0 (100)	100/100	0/0	0/0
Salmonella serogroup O9 (45)	0 (0)	0 (0)	1 (2)	11 (27)	30 (93)	3 (100)	0 (100)	0 (100)	0 (100)	100/100	0/0	0/0
Vibrio spp. (total, 92)												
V. vulnificus (15)	14 (93)	0 (93)	1 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	100/100	0/0	0/0
V. parahaemolyticus (41)	0 (0)	22 (54)	19 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	100/100	0/0	0/0
V. cholerae non-O1 (26)	10 (38)	15 (96)	1 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	100/100	0/0	0/0
Other *Vibrio* species (10)	1 (11)	4 (56)	5 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	100	0	0

[a] MICs (μg/ml) of tigecycline for *Aeromonas*, *Salmonella*, and *Vibrio* species were determined by the broth microdilution method.
[b] Category MIC values were derived from U. S. FDA and EUCAST breakpoints.

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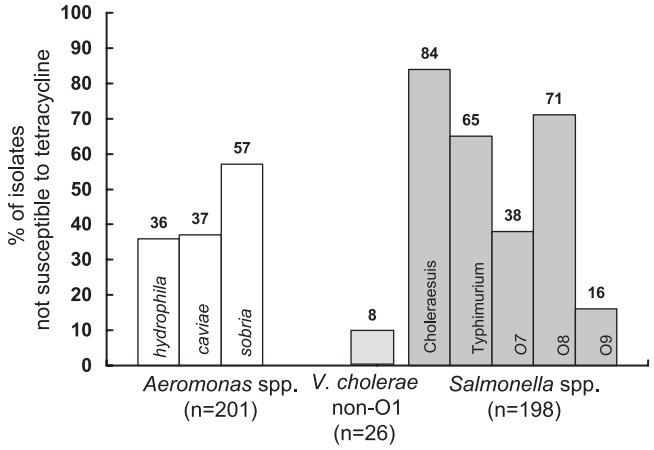

FIG. 1. Rates of isolates of *Aeromonas*, *Vibrio*, and *Salmonella* species that are not susceptible to tetracycline, as determined by the broth microdilution method.

Standards Institute (CLSI) guidelines (5). MICs of tigecycline and tetracycline were determined by the broth microdilution method (5). The range of antibiotic concentrations tested was 0.03 μg/ml to 128 μg/ml. Interpretation of tigecycline MIC results was determined according to the recommendations of the United States Food and Drug Administration (U. S. FDA) given in the package insert for treating *Enterobacteriaceae* (susceptible, ≤2 μg/ml; resistant, ≥8 μg/ml) and those recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (susceptible, ≤1 μg/ml; resistant, >2 μg/ml) (7). *Escherichia coli* ATCC 25922 was used as the control strain in each test.

All isolates of *Salmonella* species were susceptible to cefotaxime. One isolate of *V. cholerae* (non-O1 serotype) was intermediate to cefotaxime. The susceptibility rates of *A. hydrophila*, *A. caviae*, and *A. sobria* to cefotaxime were 79%, 73%, and 95%, respectively. All isolates of *Vibrio* species were susceptible to ciprofloxacin. The susceptibility rates of *A. hydrophila*, *A. caviae*, and *A. sobria* to ciprofloxacin were 90%, 86%, and 93%, respectively. Isolates of the *Salmonella* species had lower rates of susceptibility to ciprofloxacin (22% for *S. enterica* serotype Choleraesuis, 75% for *S. enterica* serotype Typhimurium, 77% for *Salmonella* serogroup O7, and 57% for *Salmonella* serogroup O8) than isolates of *Aeromonas* species, except for *Salmonella* serogroup O9 (96%).

The tigecycline MICs for the control strain were within the recommended range. All *Vibrio* and *Salmonella* isolates tested were susceptible to tigecycline, and one isolate (1.6%) of *A. caviae* was intermediate (MIC of 4 μg/ml) to tigecycline by U. S. FDA criteria (Table 1). According to EUCAST criteria, 1.2% of *A. hydrophila* isolates, 3.2% of *A. caviae* isolates, 1.6% of *Salmonella* serotype Typhimurium isolates, and 1.6% of *Salmonella* serotype Choleraesuis isolates were not susceptible to tigecycline (Table 1).

As shown in Fig. 1, four isolates (4.4%) of *Vibrio* species (tetracycline MIC range, 0.12 to 16 μg/ml; MIC_{90} of 1 μg/ml), 79 isolates (39.3%) of *Aeromonas* species (tetracycline MIC range, 0.25 to >128 μg/ml; MIC_{90} of 16 μg/ml), and 116 isolates (58.6%) of *Salmonella* species (tetracycline MIC range, 1 to >128 μg/ml; MIC_{90} of >128 μg/ml) were not susceptible to

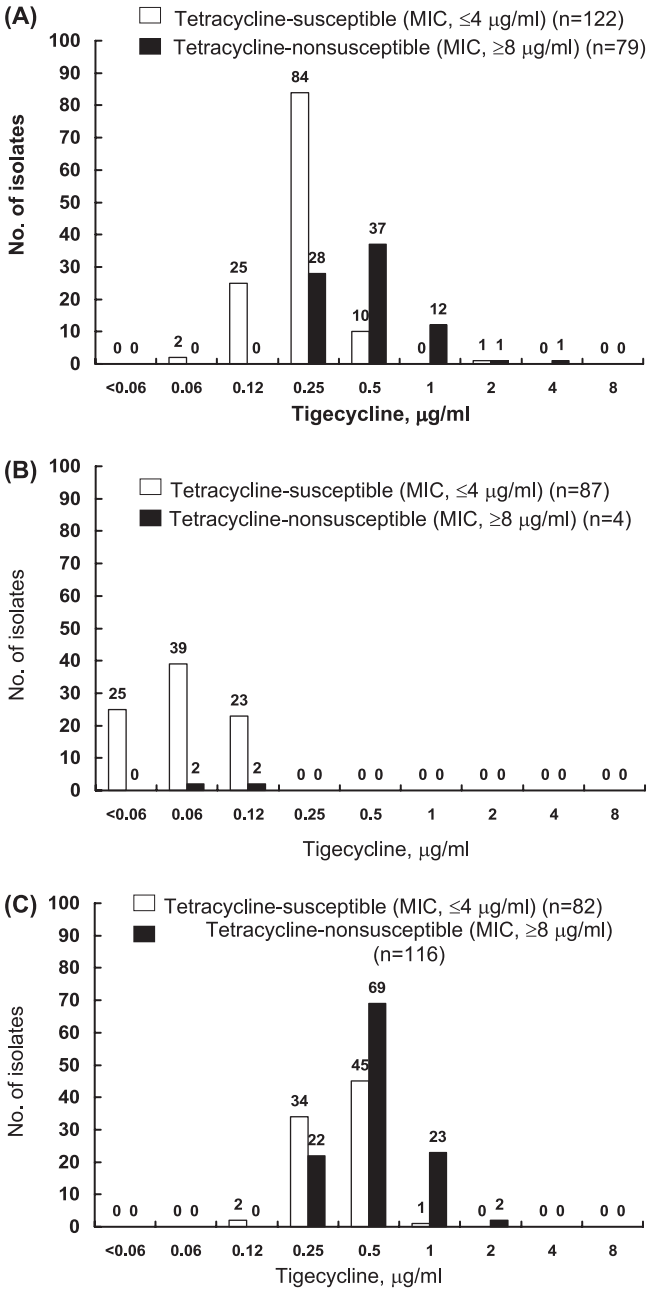

FIG. 2. Distribution of MICs of tigecycline among *Aeromonas* (A), *Vibrio* (B), and *Salmonella* (C) isolates based on their susceptibilities to tetracycline.

tetracycline by CLSI criteria (MICs of ≥8 μg/ml) (5). The MIC_{90}s of tigecycline for tetracycline-nonsusceptible isolates of *Aeromonas* species and *Salmonella* species (1 μg/ml and 1 μg/ml, respectively) were two- or fourfold higher than those for tetracycline-susceptible isolates (0.25 μg/ml and 0.5 μg/ml, respectively) (Fig. 2). The tigecycline-intermediate *A. caviae* isolate was also resistant to cefotaxime and ciprofloxacin and exhibited a tetracycline MIC of >128 μg/ml.

This study showed that tigecycline had excellent in vitro activity against clinical isolates of *Aeromonas*, *Vibrio*, and nontyphoid *Salmonella* species (NTS). Chuang et al. reported a

synergistic effect between cefotaxime and minocycline against *V. vulnificus* isolates (2, 3). Due to the low MICs of tigecycline among isolates of *V. vulnificus* and *V. parahaemolyticus* and the high concentration of tigecycline in treating skin and soft tissue infections, this agent alone or in combination may be a promising option for the treatment of infections due to *Vibrio* species (1).

Antimicrobial susceptibilities of *Aeromonas* species varied with different geographic areas and different species. In a study from North America, *A. hydrophila* was more resistant to cephalosporins and tetracycline than either *A. caviae* or *A. sobria* (13, 17). In Taiwan, Ko et al. (12) reported that the resistance rate to tetracycline was 48% for *A. hydrophila*, 58% for *A. sobria*, and 41% for *A. caviae*, rates which are much higher than in other areas. In the present study, 28.4% (46/210) of all *Aeromonas* isolates tested were not susceptible to cefotaxime, but one cefotaxime- and ciprofloxacin-resistant *A. caviae* isolate, which was highly resistant to tetracycline, was intermediate to tigecycline.

About 5% of NTS may cause invasive or systemic infections and require antimicrobial therapy (19, 22). Resistance to extended-spectrum cephalosporins among NTS has been reported globally since these isolates were recognized in the 1980s (15). In Taiwan, the ceftriaxone resistance rate among NTS isolates ranged from 0.8% to 2.1% in different serogroups (21, 22). Morosini et al. reported that five isolates of extended-spectrum β-lactamase-producing *Salmonella* species were susceptible to tigecycline (16). All of the clinical isolates of *Salmonella* species in the present study were fully susceptible to both cefotaxime and tigecycline.

The limitation of this study is that all the isolates tested were identified by conventional biochemical and serological methods. Molecular methods are more reliable than conventional methods for species identification, particularly for the identification of *Aeromonas* and *Vibrio* species.

In conclusion, the promising antimicrobial activities of tigecycline against *Aeromonas*, *Vibrio*, and *Salmonella* isolates suggest the need for further in vivo trials to determine if treatment with this agent could provide a better clinical response than responses to currently available treatment options.

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