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ORIGINAL ARTICLE

Microbial isolation and emergence of antimicrobial resistance associated with tigecycline usage

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Background: With the increasing experience of tigecycline usage, its ecological impact on microorganisms raises concerns but remains unknown. We aimed to analyze the difference in microorganisms isolated before, during, and after tigecycline usage and their susceptibility to antimicrobial agents.
Methods: Between July 2008 and August 2009, 66 patients who received tigecycline monotherapy for more than 2 days at a Taiwan medical center were enrolled. Antimicrobial susceptibility testing was performed by broth microdilution method with VITEK-2 system and was analyzed according to the Clinical and Laboratory Standards Institute guidelines, except for tigecycline. We followed USA Food and Drug Administration criteria for interpretation of susceptibility to tigecycline.
Results: The median duration of tigecycline monotherapy was 13.4 days. After tigecycline treatment, the isolation frequency of *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* decreased, but that of *Pseudomonas aeruginosa*, *Proteus* sp, and *Stenotrophomonas maltophilia* did not change. *A baumannii* and *P aeruginosa* were the two most common pathogens when tigecycline was administered. The tigecycline susceptibility rate of *A baumannii* isolates decreased after the administration of tigecycline.

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Conclusion: The most common pathogens isolated in patients receiving tigecycline were *A baumannii* and *P aeruginosa*. Tigecycline usage decreased the isolation frequency of *A baumannii*, methicillin-resistant *S aureus*, *E coli*, and *K pneumoniae*. Exposure to tigecycline may be associated with a decreased susceptibility rate of *A baumannii* for tigecycline.

Introduction

Tigecycline, a 9-*t*-butylglycylamino derivative of minocycline, is one of the latest glycylcycline antibiotics. It overcomes two common tetracycline resistance mechanisms mediated by acquired efflux pumps and ribosomal protection.[1] The characteristics of broad spectrum, relatively low toxicity, and postantibiotic effect make tigecycline an important antimicrobial agent in clinical practice.[1] In 2009, the US Food and Drug Administration (FDA) approved tigecycline for community-acquired pneumonia, as well as for intraabdominal infection (IAI) and skin and soft tissue infection.[2] It is also effective in the treatment of common multidrug-resistant gram-negative bacteria encountered frequently in hospital-acquired infections, including multidrug-resistant *Acinetobacter baumannii*,[3] *Stenotrophomonas maltophilia*,[4] and *Clostridium difficile*,[5] although it is less effective against *Pseudomonas aeruginosa*, *Proteus* sp, and *Providencia* sp.[6]

Use of many classes of antimicrobial agents has been shown to be a risk factor for the colonization of or infection by resistant pathogens. For example, extended spectrum β-lactamase-producing *Klebsiella pneumoniae* and *Escherichia coli*[7] were shown to be associated with prior use of fluoroquinolones and cephalosporins. A history of carbapenem and fluroquinolone use was found to be associated with carriage of carbapenem-resistant *P aeruginosa*.[8] The emergence of tigecycline resistance is associated with not only tigecycline usage but also ciprofloxacin exposure.[9] A case report showed increased minimal inhibitory concentration (MIC) of tigecycline during the treatment of carbapenemase-producing *K pneumoniae* with tigecycline.[10] Whether increasing level of tigecycline exposure plays a role in the selection of tigecycline-resistant pathogens still remains unknown. To investigate the ecological impact of tigecycline on microbes and the antimicrobial susceptibility of the organisms after tigecycline exposure, we retrospectively analyzed bacterial isolates from patients before, during, and after tigecycline exposure.

Materials and methods

The study was performed at a medical center in southern Taiwan between July 2008 and August 2009 after receiving approval from the hospital's Institutional Review Board. Patients were enrolled if they had received tigecycline monotherapy for more than 48 hours. Patients who received tigecycline as a part of a combination therapy were excluded to avoid the influence of the coadministrated antibiotics. Comorbidities were evaluated by Charlson Comorbidity score. The acute physiology and chronic health evaluation II score of all the enrolled patients were obtained at admission. Hospital-acquired infections were defined at the date tigecycline was administered according to the definition by Centers for Disease Control and Prevention.[11,12]

Clinical isolates were categorized into three periods depending on the time they were isolated: before-, during-, and after-tigecycline periods. All available isolates in the before-and during-tigecycline periods in the prehospital and hospitalization course were included, whereas only those collected within 2 weeks after tigecycline discontinuation were included in the after-tigecycline period. When and which specimens to collect were decided by physicians according to the clinical suspicion.

Blood culture was performed using Organon Teknika BacT/Alert system, Massachusetts, United States. Urine specimens were inoculated in sheep blood/eosin methylene blue bi-plates. Respiratory secretions (sputum, endotracheal aspirate, and bronchial lavage) were inoculated in colistin/nalidixic acid and chocolate agar. Species were identified and antimicrobial susceptibility was tested by VITEK®-2 (bioMerieux, Inc., Saint Louis County, Missouri, United States). The susceptibility testing results were interpreted according to the Clinical and Laboratory Standards Institute guidelines, except for tigecycline.[13] The USA FDA criteria were followed for susceptibility interpretation of tigecycline. The susceptibility interpretation criteria were defined as susceptible for an MIC of tigecycline of $\leq$2 μg/mL, intermediate for an MIC of 4 μg/mL, and resistant for an MIC of $\geq$8 μg/mL for gram-negative bacteria.[14] Susceptibility testing of tigecycline for Gram-positive bacteria was not regularly performed at our laboratory and was performed by disk diffusion test upon clinician's request.

Statistical analysis

All data were analyzed by statistical package for social sciences (SPSS) version 15.0 (SPSS Inc., Chicago, IL, USA). Changes in the frequencies of specific pathogens and their susceptibilities were calculated for categorical variables by using the Chi-squared test or Fisher's exact test when 20% of the expected count was less than five. A p value of less than 0.05 was considered statistically significant (two-tailed analysis).

Results

A total of 66 patients were included in this study. The dosage of tigecycline for these patients was 100 mg loading dose, followed by 50 mg every 12 hours, except for one

patient with liver cirrhosis who received half dose (25 mg every 12 hours). Their demographic characteristics are listed in Table 1. The duration of tigecycline administration ranged from 6 to 23 days (median, 13 days). Twenty-two (33.3%) cases had hospital-acquired infections. Of the 66 patients, 31 (46%) were treated empirically, and 35 were treated according to their microbiological culture results. *A baumannii* (17/35, 48.5%) was the most common isolated organisms.

Skin and soft tissue infection (22 patients, 33%) was the most common infection site, followed by pulmonary infection (20 patients, 30%) and IAI (17 patients, 25.7%). Sixty-four (96%) patients survived for more than 2 weeks, and 56(85%) patients survived during hospitalization. Five patients died during tigecycline treatment and were excluded from the data in the after-tigecycline period.

The antimicrobial agents used in the before-tigecycline period are presented in Table 2. Before tigecycline administration, most (41, 62%) of the patients received less than 2 antibiotics, and 12 (18%) patients received more than three antibiotics. Meropenem and piperacillin/tazobactam were the most commonly used antibiotics before tigecycline use.

Selection of microorganisms after tigecycline usage

Patient numbers of each common microorganism isolated in the three separate periods are listed in Table 3. *A baumannii*, *P aeruginosa*, and *K pneumoniae* were the three most common pathogens during tigecycline treatment. Five cases (7.5%) had isolation of bacterial strains other than those causing their primary infections.

P aeruginosa was isolated from 7 (10.6%) and 12 (18.18%) patients before and after tigecycline use, respectively ($p = 0.11$, odds ratio [OR]: 0.53, 95% confidence interval [CI]: 0.74—5.94). Between before and after tigecycline use, *A baumannii* isolates decreased from 25% to 7% ($p < 0.005$, OR: 0.26, 95% CI: 0.08—0.73). The frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) ($p < 0.05$, OR: 0.32, 95% CI: 0.098—1.09), *E coli* ($p < 0.05$, OR: 0.12, 95% CI: 0.01—0.52), and *K pneumoniae* ($p < 0.05$, OR: 0.28, 95% CI: 0.08—0.81) also decreased after tigecycline exposure. Tigecycline had no significant impact on the isolation frequency of *Stenotrophomonas maltophilia* ($p = 0.09$, 95% CI: 0.11—1.51), *Proteus* sp ($p = 0.23$, 95% CI: 0.06—3.08), *Enterococcus* sp ($p = 0.23$, 95% CI: 0.04—1.68), and *Candida* sp ($p = 0.09$, 95% CI: 0.08—1.75) in after-tigecycline period.

Changes in antibiotic susceptibility

At a median of 13 days after tigecycline treatment, the tigecycline susceptibility rate decreased from 86% (before-tigecycline) to 54% (after-tigecycline) in *A baumannii* ($p = 0.04$, OR: 0.2, 95% CI: 0.04—0.91) (Table 4). The susceptibility to tigecycline for *K pneumoniae* and *E coli* between before and after tigecycline usage was not significantly different.

The susceptibility rates to antimicrobial agents for Gram-negative isolates at each period are presented in Table 5. Of the 22 strains of *A baumannii*, nine (40.9%) remained susceptible to tigecycline but were isolated during tigecycline treatment. Susceptibility rate was less than 41% for all antimicrobial agents in the during-

Table 1 Demographics and characteristics of the 66 cases receiving tigecycline

Characteristics	Mean	SD
Age (yr)	68.4	17.7
Comorbidity score	5.7	3.0
APACHE II score	11.4	3.1
Duration of tigecycline administration (d)	13.4	4.9
Average admission duration before tigecycline use (d)	7.6	4.0
Gender, *n* (%)		
Male	40	60.6
Female	26	39.3
Source, *n* (%)		
Community-acquired	38	57.6
Health care-related	6	9.1
Hospital-acquired	22	33.3
Underlying disease, *n* (%)		
Liver cirrhosis	1	1.5
ESRD	2	3.0
CHF (grade 3, grade 4)	8	12.1
Diabetes mellitus	27	40.1
Malignancy	14	21.2

APACHE = acute physiology and chronic health evaluation; CHF = congestive heart failure; ESRD = end stage renal disease; SD = standard deviation.

Table 2 Antimicrobial treatment administered before tigecycline in 66 cases

Antimicrobial treatment	Patient number
Piperacillin/tazobactam	36
Meropenem	28
Vancomycin	23
Ceftazidime	21
Fluconazole	11
Ampicillin/subactam	14
Ciprofloxacin	18
Levofloxacin	23
Teicoplanin	9
Eertapenem	7
Aamoxicillin/clavulanate	7
Cefpirome	5

tigecycline period. Susceptibility rate after discontinuation of tigecycline was the highest for meropenem (46.2%) compared with the other antibiotics. All Gram-positive bacteria collected in the three periods remained susceptible to vancomycin.

Discussion

Our study focuses on the ecological impact of tigecycline exposure in real world practice and is different from the study designs that focused on volunteer[15] and association studies on drug usage amount and resistance trends.[16] We found that the frequency of *A baumannii*, MRSA, *E coli*, and *K pneumoniae* isolates decreased significantly after tigecycline usage. A previous study on healthy volunteers revealed that, after 8 days of tigecycline exposure, the stool colonization rates of *E coli* and *Enterococcus* sp reduced, whereas the rate of yeasts increased.[15] Our study is different from other studies in the following respects: (1) clinical infections but not fecal colonization were studied and (2) effect of the antimicrobials other than tigecycline that may have been prescribed before the initiation of tigecycline treatment in clinical practice was not analyzed in this study. Beside the changes in common pathogens isolated after tigecycline usage, *A baumannii* and *P aeruginosa* were the two most common bacteria during the tigecycline usage period.

The superinfection rate with tigecycline usage ranged from 2.4% to 23.5% across different studies.[17,18] Garcia-Cabrera et al.[17] had reported that *P. aeruginos*a caused 58.5% superinfections at an average of 8 days of tigecycline treatment for nosocomial infections. Five cases (7.5%) in the study had bacterial isolation other than those causing their primary infections. However, there was no increase in the isolation rate of *P aeruginosa* in our study, although it ranked the first among the most frequent pathogens in hospital-acquired infections and was responsible for 12.4% (148/1186) of the cases reported in the study hospital in 2009 (Data from Infection Control Committee). Unlike in a previous study,[17] in this study, we included not only cases of nosocomial infection. Besides, many cases in the study received antipseudomonal antibiotics before tigecycline treatment.

*Candid*a infection has been considered a poor prognostic factor in IAIs.[19] Broad-spectrum antibiotics, such as carbapenem[20] and tigecycline,[21] influence normal gut flora and

Table 3 Isolated microorganisms by patient number in the three separate periods

Isolated microorganisms	Before, *n* (%)	During, *n* (%)	After, *n* (%)
	n = 66	*n* = 66	*n* = 61
A baumannii[a,b]	17 (25.8)	6 (9.0)	5 (8.2)
P aeruginosa	7 (10.6)	6 (9.0)	12 (19.7)
E coli[a,b]	14 (21.2)	1 (1.5)	2 (3.3)
K pneumoniae[a,b]	16 (24.2)	5 (7.6)	5 (8.2)
MRSA[a,b]	11 (16.7)	2 (3.0)	4 (6.6)
Enterococcus	6 (9.0)	1 (1.5)	2 (3.3)
S maltophilia[b]	9 (13.6)	1 (1.5)	4 (6.6)
Candida species	7 (10.6)	2 (3.0)	3 (4.9)
CoNS	5 (7.6)	3 (4.5)	1 (1.6)
Proteus species	4 (6.0)	1 (1.5)	2 (3.3)
Prevotella species	2 (3.0)	0 (0.0)	0 (0.0)

[a] Significantly decreased isolation frequency between "after-tigecycline" and "before-tigecycline" groups
[b] Significantly decreased isolation frequency between "during-tigecycline" and "before-tigecycline" groups.
CoNS = Coagulase-negative *Staphylococcus*; MRSA = methicillin-resistant *Staphylococcus aureus*.

Table 4 Changes in isolate number and their tigecycline susceptibility of *A baumannii*, *E coli*, and *K pneumoniae* in the three periods

	A baumannii	*E coli*	*K pneumoniae*
Before			
Isolate No.	35	15	20
Susceptibility (%)	86	100	95
During			
Isolate No.	9	1	3
Susceptibility (%)	67	100	67
After			
Isolate No.	11	2	5
Susceptibility (%)	54	50	60

Table 5 The antimicrobial susceptibility rates to Gram-negative pathogens in the three periods

	Before, *n* (%)	During, *n* (%)	After, *n* (%)
Susceptibility	92	22	39
Tigecycline	65 (70.1)	9 (40.9)	13 (33.3)
Meropenem	52 (56.5)	9 (40.9)	18 (46.2)
Piperacillin/tazobactam	32 (34.8)	9 (40.9)	14 (35.9)
Ciprofloxacin	28 (30.4)	8 (36.4)	11 (28.2)
Levofloxacin	33 (35.9)	9 (40.9)	11 (28.2)
Ceftazidime	26 (28.2)	7 (31.8)	15 (38.5)
Cefpirome	28 (30.4)	7 (31.8)	15 (38.5)

have been known to increase *Candida albicans* colonization in the gut in an animal study; however, this finding does not indicate the occurrence of clinical *Candida* infection.[22] The impact of tigecycline on gut colonization was not assessed in this study. Our results revealed that tigecycline did not increase infections with clinical *Candida* species.

In the study, *A baumannii* was the most common pathogen for which tigecycline was prescribed. We found that 45% of the *A baumannii* isolated in the before-tigecycline period were carbapenem-resistant. Tigecycline was reported to have similar MIC_{50} and MIC_{90} in both imipenem-sensitive and imipenem-resistant *Acinetobacter* sp.[22] Because 57% of *A baumannii* causing nosocomial infections in 13 Taiwan intensive care units were resistant to carbapenem,[23] tigecycline, colistin, or sulbactam is still considered as an important treatment option. Although tigecycline has not been approved for hospital-acquired pneumonia, some studies report excellent tissue penetration in murine epithelial lung fluid of tigecycline[24] and its efficacy in *Acinetobacter* sp.[3,22] Moreover, decreased activity of tigecycline against *A baumannii*, as was found in this study and was reported in a previous study,[17] should be considered for patients with persistent *A baumannii* infection because we noted *A baumannii*, secondary to *P aeruginosa*, as one of the important superinfection pathogens during tigecycline treatment. To avoid the selection of tigecycline-resistant *A baumannii*, some authorities suggest a higher mutant prevention concentration in the treatment of carbapenem-resistant *A baumannii*.[25] In view of the fact that high dose of tigecycline usage has not been approved by the US FDA, combination antimicrobial therapy has been suggested to avoid tigecycline-resistant strains during treatment.[26] Because no single antibiotic has a susceptibility rate of more than 50% during- and after-tigecycline treatment periods, combination therapy may be considered in clinical practice when patients with infection symptoms and signs are encountered during tigecycline therapy.

Our study has the following limitations. Microorganisms isolated before-tigecycline and after-tigecycline periods could have been affected by the administrated antimicrobials at both the periods. Besides, specimens were collected on the basis of physician's decision rather on the basis of a regular culture procedure at fixed intervals.

In conclusion, we revealed that an average of 13.4 days exposure of tigecycline was associated with a decreased isolation frequency of *A baumannii*, MRSA, *E coli*, and *K pneumoniae*. *A baumannii* and *P aeruginosa* should be considered when clinicians choose empirical treatment for patients failing to respond to tigecycline because they were the most common pathogens in patients receiving tigecycline. Decreased susceptibility of *A baumannii* for tigecycline may occur in the process of tigecycline therapy.

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