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Activity of Tigecycline Tested Against Vancomycin-resistant Enterococci, Including Clonal Complex-17 *E. faecium* Strains, Isolated in Europe

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ABSTRACT

Objectives:

To evaluate the activity of tigecycline when tested against clinical strains of enterococci collected in European medical centers, including *E. faecium* strains characterized as being clonal complex 17 (CC-17). CC-17 characterizes a lineage of *E. faecium* with resistance (R) to ampicillin (AMP) and ciprofloxacin (CIP) with or without R to vancomycin (VANC), a pathogenicity island and an association with hospital outbreaks, which have spread globally.

Methods:

Enterococcal strains were submitted from 34 medical centers located in Europe (13 countries) and Israel during 2000-2007. Strains were susceptibility (S) tested against tigecycline and >20 antimicrobials using CLSI broth microdilution methods and USA-FDA/EUCAST interpretative criteria (tigecycline S at ≤0.25 mg/L). VanA *E. faecium* strains R to AMP and CIP were characterized as a CC-17. A subset of CC-17 strains were further characterized by PFGE and PCR for *esp* gene.

Results:

4,591 enterococcal strains (7.1% VANC-R) were collected, including 3,070 *E. faecalis* (1.6% VANC-R) and 1,337 *E. faecium* (22.3% VANC-R). VANC-R was observed in 27 (79.4%) centers (all countries surveyed). Higher rates of VANC-R were found in Germany, Ireland and the United Kingdom. High level gentamicin R was observed in 33.3% of *E. faecalis* and 40.9% of *E. faecium*, while only 73.5% of *E. faecium* were S to quinupristin/dalfopristin. Tigecycline was very active against enterococci (MIC_{90}, 0.25 mg/L; 97.3% S), including VANC-R *E. faecium* (MIC_{90}, ≤0.12 mg/L; 99.7% S) and *E. faecalis* (MIC_{90}, 0.25 mg/L; 94.0% S) strains (see Table). Tigecycline was also highly active against VANC-R *E. faecium* CC-17 phenotype strains (MIC_{90}, ≤0.12 mg/L; 100.0% S).

See Table 1.

Conclusions:

Tigecycline was very active against strains of enterococci causing infections in European hospitals and its activity was not adversely affected by R to VANC or other antimicrobials. This novel glycylcycline represents an important therapeutic option for infections caused by vancomycin-resistant enterococci, including the epidemic *E. faecium* CC-17 strains.

INTRODUCTION

Enterococcus spp. is the fourth most commonly isolated bloodstream infection (BSI) pathogen (7.5 %) in Europe and the third most common in the United States (USA). Isolation of vancomycin-resistant enterococci (VRE) has consistently increased in the USA and has become endemic in many medical centers. Isolates of VRE are now increasing in some European countries that we have monitored over the past decade. An observation from early years of the SENTRY Antimicrobial Surveillance Program (1997-1999) illustrated that vancomycin resistance rates were considerably higher in USA compared to other regions of the world.

The increased use of vancomycin for treatment of oxacillin-resistant *Staphylococcus* spp. has been a leading factor for selection of these resistant *Enterococcus* phenotypes. Clonal dissemination and various environmental gene pools such as possibly animal healthcare sources in Europe may have also contributed to the spread of VRE. VRE infections occur most commonly among immunocompromised patients, hospitalized patients with multiple co-morbidities and those in ICUs, nursing homes or being treated with multiple antimicrobial agents. High morbidity and mortality has been associated with VRE infections due to limited therapeutic options and acquisition of virulence genes.

Tigecycline is the first glycylcycline used in clinical practice. This agent has broad-spectrum coverage of Gram-positive pathogens, many Enterobacteriaceae, anaerobic bacteria and some non-fermentative Gram-negative bacilli. The USA Food and Drug Administration (USA-FDA) has approved tigecycline for treatment of skin and soft tissue infections and intra-abdominal infections. Treatment of these types of infections can be complicated by VRE as a primary or secondary pathogen.

MATERIALS AND METHODS

Nearly 4,600 isolates of *Enterococcus* spp. were collected from European medical centers for antimicrobial susceptibility testing during 2000 to 2007. Included among these isolates were *E. faecalis* (3,070 strains; 50 vancomycin non-susceptible) and *E. faecium* (1,337 strains; 298 vancomycin non-susceptible). These strains were referred by 34 medical centers in Europe and Israel to a central laboratory for identification confirmation and susceptibility testing. Isolates were tested for susceptibility to antimicrobial agents including tigecycline and nine comparator agents using the CLSI broth microdilution method (M7-A7, 2006). Mueller-Hinton broth was used to inoculate commercially prepared panels (TREK Diagnostics, Cleveland, OH, US). Susceptibility determinations were determined using the CLSI (M100-S18) and EUCAST clinical breakpoint criteria.

Isolates of vancomycin-resistant (vanA) *E. faecium* were characterized as CC-17 if they were also resistant to ampicillin and ciprofloxacin. This included a collection of 162 strains. There were 1,247 isolates used to determine the rate of VRE between 2000 and 2007 which were collected from infection sources that have been monitored each study year. These included BSI, respiratory tract infections and skin and skin stucture infections.

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RESULTS

- Tigecycline inhibited 99.9% of *Enterococcus* spp. strains at ≤0.5 mg/L, regardless of resistance phenotype (Table 1). Only 2.7% of isolates had a non-susceptible MIC value (>0.25 mg/L).
- Tigecycline was highly active against *E. faecalis* (MIC_{90}, 0.25 mg/L) and *E. faecium* (MIC_{90}, ≤ 0.12 mg/L) isolates (Table 2). This potency was greater than all other tested comparator agents.
- Linezolid was active against most isolates of *E. faecalis* and *E. faecium* (>99%). However, the rate of vancomycin- and quinupristin/dalfopristin-resistant *E. faecium* was over 22% when applying either the CLSI or EUCAST susceptibility breakpoints (Table 2).
- One-third to one-half of the tested isolates showed high-level resistance to aminoglycosides, negating the synergistic interaction between this class and ß-lactams or vancomycin (Table 2).
- Vancomycin resistance ranged from 0.0 to 65.2% in the monitored European countries with highest levels detected in Ireland and the United Kingdom (Table 3). This table also shows a considerable variation in resistance to quinupristin/dalfopristin with rates ranging from 0.5 to 44.1%. Resistance to tigecycline was low in most monitored countries.
- Figure 1 illustrates that vancomycin resistance increased from a level of only 5% for 2000 and 2001 to 10% for 2002 and 2003. A steady increase over the next three years illustrates that vancomycin resistance has now reached approximately 20% in Europe between 2006 and 2007. These rates are most similar to those observed in the USA 5-8 years earlier.

Table 1. Tigecycline MIC population distribution for *Enterococcus* spp. isolated in European medical centers (2000-2007).

Organism (no. tested)	Cumulative % inhibited at tigecycline (MIC mg/L) ≤0.12	0.25	0.5	1	No. of non-susceptible strains (%)
All Enterococci (4,591)	75.5	97.3	99.9	100.0	124 (2.7)
E. faecalis					
Vancomycin-S[a] (3,020)	68.6	96.9	99.9	100.0	95 (3.1)
Vancomycin-non-S (50)	60.0	94.0	100.0	-	3 (6.0)
E. faecium					
Vancomycin-S (1,039)	89.9	98.6	99.8	100.0	15 (1.4)
Vancomycin-non-S (298)	94.6	99.7	100.0	-	1 (0.3)
CC-17 Vancomycin phenotype (162)	96.3	100.0	-	-	0 (0.0)

a. S = susceptible.

Table 2. Potency and susceptibility of tigecycline and nine comparator agents tested against *Enterococcus* spp. collected from patients in European medical centers.

Organism (no. tested)	Antimicrobial agent	MIC (mg/L) 50%	90%	% susceptible[a] CLSI	EUCAST
E. faecalis (3,070)	Tigecycline	≤0.12	0.25	96.8	96.8
	Ampicillin	≤2	≤2	99.3	-[b]
	Levofloxacin	1	>4	66.2	-
	Ciprofloxacin	1	>4	62.4	-
	Gentamicin (HL)[c]	≤500	>1000	66.7	-
	Streptomycin (HL)	≤1000	>2000	62.8	-
	Quinupristin/dalfopristin	>2	>2	1.1	1.1
	Linezolid	1	2	>99.9	100.0
	Teicoplanin	≤2	≤2	98.7	98.7
	Vancomycin	1	2	98.4	98.4
E. faecium (1,337)	Tigecycline	≤0.12	≤0.12	98.8	98.8
	Ampicillin	>16	>16	10.5	-
	Levofloxacin	>4	>4	18.2	-
	Ciprofloxacin	>4	>4	5.5	-
	Gentamicin (HL)	≤500	>1000	59.1	-
	Streptomycin (HL)	≤2000	>2000	47.5	-
	Quinupristin/dalfopristin	1	>2	73.5	73.5
	Linezolid	1	2	99.7	99.9
	Teicoplanin	≤2	>16	83.8	82.9
	Vancomycin	1	>16	77.7	77.7

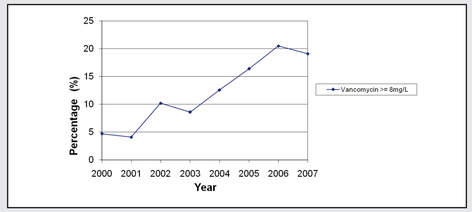
a. Susceptibility percentages were based upon those recommended by the CLSI (M100-S18, 2008) and EUCAST clinical breakpoints.
b. - = no established criteria.
c. HL = high-level.

Table 3. Resistance rates observed among *E. faecium* isolates collected from the monitored countries in Europe, Israel and Turkey.

Country (no. tested)	% resistant by antimicrobial agent[a] Vancomycin	Quinupristin/dalfopristin	Tigecycline
Belgium (31)	9.7	25.8	0.0
France (85)	3.5	37.7	1.2
Germany (320)	22.5	39.4	0.3
Greece (20)	20.0	0.5	0.0
Ireland (164)	65.2	17.1	0.6
Israel (29)	34.5	17.2	3.4
Italy (114)	15.8	29.0	0.9
Poland (66)	22.7	9.1	7.6
Spain (60)	5.0	43.3	3.3
Sweden (102)	3.9	44.1	0.0
Switzerland (29)	0.0	41.4	0.0
Turkey (247)	9.3	10.5	1.6
UK (68)	52.9	8.8	0.0

a. Percentages represent the non-susceptibility rates using the CLSI breakpoint criteria (M100-S18, 2008) for vancomycin and quinupristin/dalfopristin and USA-FDA/EUCAST breakpoints for tigecycline.

Figure 1. Vancomycin resistance rates in Europe over the last eight years of surveillance (SENTRY Program).



CONCLUSIONS

- Isolation of vancomycin-resistant *Enterococcus* spp. from human infections has significantly increased in European countries over the past four years and quinupristin/dalfopristin resistance is now an important problem among *E. faecium* isolates in many of the monitored countries.
- Epidemic MDR-*E. faecium* isolates were detected across nearly all countries in Europe, and many of these strains were phenotypically consistent with CC-17. Tigecycline has potent activity against these problematic MDR and CC-17-like isolates of *E. faecium.*
- Along with traditional or newer agents such as linezolid, tigecycline has emerged as a valuable treatment modality for *Enterococcus* spp. including MDR-*E. faecium*.