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Characteristics of Tedizolid Non-susceptible Enterococcal Clinical Isolates

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ABSTRACT

Background:

Tedizolid is a novel oxazolidinone antibiotic with activity across a broad range of gram-positive pathogens. The aim of this study was to describe the clinical, microbiological and genomic characteristics of tedizolid (TZD) resistant enterococcal clinical isolates.

Methods:

Tedizolid resistant isolates were recovered from patients at Westchester Medical Center, NY from 2012 to 2016. In vitro susceptibility of tedizolid was performed by broth microdilution using the Sensititre™ panel in accordance with the guidelines of the Clinical and Laboratory Standards Institute. The sequence type (ST) of enterococci was determined based on multilocus sequence typing (MLST) data derived from assembled next-generation sequencing.

Results:

During the study period, we identified 8 clinical isolates which were resistant to tedizolid. 7/8 isolates were *E. faecium* belonging to a unique ST736 which predominates in our hospital. 7/8 isolates showed G2567T mutation of 23S rRNA. Only one patient had prior receipt of Linezolid. None of the patients had received tedizolid in past.

Conclusion:

There is possible de-novo emergence of tedizolid resistant enterococcal isolates. This highlights the need for further improvement in infection control practices and evaluation of newer options for the treatment of enterococcal infections.

INTRODUCTION

Westchester Medical Center (WMC) is a tertiary care, academic teaching hospital located in suburban New York City. With a patient population inclusive of those who have undergone solid organ transplantation and hematopoeitic stem cell transplantation (HSCT), the immunocompromised patients at our hospital are at high risk for colonization and infections with resistant gram positive organisms, including multi-drug resistant enterococci.

In 2014, the VRE rate at WMC was noted to be 27.1% hospital wide. The daptomycin non-susceptibility rates amongst VRE isolates and non-VRE isolates were observed to be 27%, and 2%, respectively. Tedizolid is a novel oxazolidinone antimicrobial agent with potent activity against a broad range of Gram-positive organisms. Linezolid (LIN) and Tedizolid (TZD) have been used recently for treatment of Daptomycin non-susceptible *enterococci* (DNSE) infections. The aim of this study was to define the clinical, microbiological and genomic characteristics of tedizolid resistant enterococcal isolates.

MATERIALS AND METHODS

Tedizolid resistant enterococcal isolates were recovered from patients at Westchester Medical Center, NY from 2012 to 2016. In vitro susceptibility of these isolates was performed by broth microdilution using the Sensititre™ panel in accordance with the guidelines of the Clinical and Laboratory Standards Institute. The sequence type (ST) of enterococci was determined based on multilocus sequence typing (MLST) data derived from assembled next-generation sequencing.

Data was collected regarding clinical characteristics, antibiotic treatment, presence or absence of a possible source and outcome.

Patients were treated based on clinical presentation and duration of therapy was based on initial clinical and microbiological response.

RESULTS

	Date	Site	Sequence type	Prior Linezolid use	MIC mg/L				Treatment	Outcome
					LIN	TZD	DAP	VAN		
62/F	2012	Urine	736	No	8	1	16	1	NA	-
59/F	2013	Peritoneum	736	Yes	8	2	6	>16	Daptomycin x 14 d	Cure
61/F	2013	Blood	NA	No	>8	2	4	2	Tigecycline x 4 d, Doxycycline x 10 d	Cure
80/M	2015	Urine	736	No	16	1	2	>16	Daptomycin x 7 d	Cure
47/F	2015	Urine	736	No	8	1	4	>16	Daptomycin x 21 d	Cure
72/F	2015	Urine	736	No	8	1	8	>16	NA	-
75/M	2015	Urine	736	No	8	2	4	>16	NA	-
60/F	2016	Peritoneum	736	No	16	2	3	>16	Daptomycin x 21 d	Cure

- 7/8 isolates were *E. faecium* belonging to a unique ST736 which predominates in our hospital
- All these isolates were distinct with no clear nosocomial transmission based on clinical, epidemiological and genomic evidence
- 7/8 isolates showed G2567T mutation of 23S rRNA, which is known to be associated with linezolid resistance
- Only one patient had prior receipt of linezolid
- None of the patients had received tedizolid in past
- 5/8 patients required treatment with antibiotics for varied infection; All of these patients had clinical and microbiological cure
- 3/8 patients were not treated for asymptomatic bacteriuria

DISCUSSION

Enterococcus is one of the leading cause of nosocomial infections including bacteremia, intra-abdominal infections and urinary tract infections in immunocompromised patients.

Attributable mortality, when isolated from blood, is up to 36%.

Tedizolid demonstrates antimicrobial activity across a broad range of Gram-positive pathogens and greater potency than linezolid against wild-type and drug-resistant pathogens, including linezolid-resistant *Staphylococcus aureus* strains possessing mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins L3 or L4. Tedizolid has a significant potency advantage over linezolid-resistant strains carrying the horizontally transferable *cfr* gene. Methylation of A2503 of 23S rRNA by the Cfr methyltransferase confers resistance to linezolid (and other 50S ribosomal subunit–targeted antibiotics) but not to tedizolid because of structural differences in A-ring C5 substituents between the 2 drugs.

The greater potency, improved resistance and safety profile of tedizolid compared with linezolid provides the microbiological basis for its potential use in patients with infections caused by VRE/DNSE.

Recently, we showed that Tedizolid can be successfully used to treat enterococcal infections including VRE and DNSE bacteremia.

CONCLUSION

There is possible de-novo emergence of Tedizolid resistant enterococcal isolates.

This highlights the need for further improvement in infection control practices to prevent any nosocomial spread of this resistant organism.

Further studies are needed to find the mechanism of resistance to Tedizolid and for evaluationg newer options for the treatment of multi-drug resistant enterococcal infections.

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