Risk Factors and Outcomes Associated with Daptomycin-Resistant Enterococcal Infection

Kristy Tsau, PharmD[1], Jihye Kim, PharmD[1], Michael Katzman, MD, FIDSA[2]

[1]Department of Pharmacy, [2]Department of Medicine (Division of Infectious Diseases), Penn State Milton S. Hershey Medical Center, Hershey, PA

Corresponding contact information
Jihye Kim, Pharm.D.
jkim6@hmc.psu.edu

BACKGROUND

- Development of vancomycin-resistant enterococci (VRE) infections creates treatment dilemmas due to limited antimicrobial options. Although there are limited data available on the efficacy of daptomycin for the treatment of VRE infections, daptomycin is often used due to its bactericidal activity against VRE. Daptomycin is a cyclic lipopeptide that is indicated for the treatment of complicated skin and skin structure infections and endocarditis caused by *Staphylococcus aureus*.[1]
- In the past decade, emergence of daptomycin-nonsusceptible enterococci (DNSE) has been reported from multiple institutions in the United States, bringing new clinical challenges[1-6]. Enterococcal infections are one of the leading causes of nosocomial infections and remain a public health concern[2-3]. To date, risk factors and mechanism for the development of daptomycin resistance are unknown.
- The purpose of this study was to describe the characteristics, potential risk factors, and outcomes of patients with confirmed DNSE infections.

OBJECTIVES

- Primary objective: describe the characteristics of patients with DNSE infections at Penn State Hershey Medical Center (PSHMC).
- Secondary objectives: identify the potential risk factors and describe the clinical outcomes of patients with DNSE infections.

METHODS

- This was a single-center, retrospective chart review involving cultures between June 1, 2010 and August 31, 2012.
- Inclusion criteria: Age ≥18 years old, *Enterococcus* isolates that were resistant to daptomycin with confirmation by E-test (MIC>4).
- Definitions:
  - Clinical cure: clinical improvement based on review of temperatures, white blood cell (WBC) counts, and rates of re-admission within 30 days.
  - Microbiological cure: no growth in repeat culture.
  - Previous daptomycin exposure: received daptomycin within 6 months of initial positive culture.

RESULTS

Table 1. PATIENT SUMMARY

PT #	Age, Sex	Co-morbidities	Source	Species	Previous Use of Daptomycin	Invasive Devices at the Time of Initial DNSE Culture	30-Day Mortality
1	59, F	DM	Urine	*E. faecium* NON-VRE	No	Peripheral	No
2	51, F	SCT	Blood	*E. faecium*	No	Tunneled	No
3	34, F	GI	Wound	*E. faecium*	No	Tunneled, Drains	No
4	72, F	CVD, DM, GI	Blood	*E. faecium*	No	Peripheral, Non-Tunneled, Drains	Yes
5	59, F	DM, GI, SOT	Pleural Fluid	*E. faecium* NON-VRE	6 mg/kg/day x 22 d	Peripheral, PICC, Drains	No
6	71, M	GI, M	Pelvic Fluid	*E. faecium*	No	Peripheral, PICC, Drains	No
7	62, M	GI, M	Wound (Chest)	*E. faecium*	No	Peripheral, Tunneled	Yes
8	62, F	CKD, GI, SOT	Urine	*E. faecium*	No	PICC	No
9	82, F	CKD, CVD, GI	Urine	*E. faecium*	No	Peripheral, PICC, Tunneled, Dialysis	No
10	44, F	M, SCT	Blood	*E. faecium*	No	Peripheral, Tunneled	Yes
11	56, M	CKD, CVD, DM	Wound (Stump)	*E. faecium* NON-VRE	6 mg/kg/day x 8 d	Peripheral, PICC	No
12	28, F	SOT	Urine	*E. faecium*	No	Peripheral, PICC, Non-Tunneled	No
13	51, M	CKD, GI, SOT	Blood	*E. faecium*	No	Peripheral, PICC, Non-Tunneled, Drains, Dialysis	No
14	65, M	CVD, DM, SCT, M	Blood	*E. faecium*	No	Peripheral, Tunneled, Drains, Dialysis	No
15	65, M	M	Blood	*E. faecium*	6-8 mg/kg/day x 12 d	PICC	No
16	43, F	M, SCT	Blood	*E. faecium*	No	Non-Tunneled	Yes
17	31, F	M	Blood	*E. faecium*	No	Peripheral, Tunneled, Dialysis	No
18	68, F	CKD, CVD, DM, M	Wound (Abdomen)	*E. faecium*	4 mg/kg/day x 6 d	Peripheral, Non-Tunneled, Dialysis, Nephrostomy	No
19	61, F	SCT	Blood	*E. faecium* NON-VRE	No	Peripheral, Tunneled	No

CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; d: days; DM: Diabetes Mellitus; GI: Gastrointestinal; M: Malignancy; PICC: Peripherally-Inserted Central Catheter; PT: Patient; SCT: Stem Cell Transplant; SOT: Solid Organ Transplant;

Table 2. ANTIMICROBIAL SUSCEPTIBILITY OF *E. FAECIUM* ISOLATES

Enterococcus Species	DAP %	VAN %	AMP %	LZD %
E. faecium (N=19)	0	21	0	100*

DAP: Daptomycin; VAN: Vancomycin; AMP: Ampicillin; LZD: Linezolid
* Only 18 isolates had linezolid susceptibility result available

Table 3. DURATION OF INVASIVE DEVICE PRIOR TO POSITIVE CULTURE

Invasive Device (Number)	Median (Days)	Range (Days)
Peripheral Line (14)	3	1-6
PICC (8)	15	5-26
Tunneled Catheter (8)	16	4-41
Drains (6)	7	1-27
Non-Tunneled Catheter (5)	11	3-20
Dialysis Catheter (4)	13	2-21
Nephrostomy Tube (1)	59	-

SUMMARY

- We identified 19 adult patients with E-test-confirmed DNSE cultured from at least one sample over a 27-month period.
- Bacteremia was the most common type of infection among these patients (47%), followed by urine and wound infections (21% each).
- All 9 patients with bacteremia had vascular access devices, which had been in for a median duration of 22 days (range 8 – 49 days).
- Underlying diseases in these patients included malignancy (42%), gastrointestinal disease (42%), and diabetes (32%), with several patients having more than 1 comorbidity.
- All of the DNSE isolates were *E. faecium*, including 15 of 19 (79%) that also were vancomycin-resistant.
- Only 4 of the 19 patients (21%) had prior daptomycin exposure.
- Vancomycin was the most common empiric Gram-positive therapy (53%), and most patients were switched to linezolid (68%).
- Fifteen of the patients (79%) survived the index hospitalization.
- Of the 4 patients who expired, 3 had DNSE bacteremia and 1 had DNSE wound infection. None of the 4 who expired had a history of VRE or previous exposure to daptomycin; however, 3 of 4 had a prior or concurrent Gram-negative infection and all 4 had daptomycin-nonsusceptible VRE.

CONCLUSIONS

- Nonsusceptibility to daptomycin was observed in many isolates of *E. faecium*, most often in the absence of exposure to daptomycin.
- DNSE bacteremia was the most common type of infection and was associated with prolonged use of vascular access devices.
- The presence of malignancy, gastrointestinal disease, and diabetes appear to be risk factors for DNSE infection.

REFERENCES

1. Sader HS, Moet GJ, Farrell DJ, Jones RN. Antimicrobial susceptibility of daptomycin and comparator agents tested against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci: trend analysis of a 6-year period in US medical centers (2005-2010). *Diagn Microbiol Infect Dis.* 2011;70:412-416.
2. Kamboj M, Cohen N, Gilhuley K, Babady NE, et al. Emergence of daptomycin-resistant VRE: experience of a single institution. *Infect Control Hosp Epidemiol.* 2011;32(4):391-394.
3. Long JK, Choueiri TK, Hall GS, Avery RK, et al. Daptomycin-resistant Enterococcus faecium in a patient with acute myeloid leukemia. *Mayo Clin Proc.* 2005;80(9):1215-1216.
4. Sabol K, Patterson JE, Lewis II JS, Owens A, et al. Emergence of daptomycin resistance in Enterococcus faecium during daptomycin therapy. *Antimicrob Agents Chemother.* 2005;49(4):1664.
5. Kelesidis T, Humphries R, Uslan DZ, Pegues D. De novo daptomycin-nonsusceptible enterococcal infections. *Emerg Infect Dis.* 2012;18(4):674-676.
6. Green MR, Anasetti C, Sandin RL, Rolfe NE, et al. Development of daptomycin resistance in a bone marrow transplant patient with vancomycin-resistant Enterococcus durans. *J Oncol Pharm Practice.* 2006;12:179-181.

Disclosures: Kristy Tsau, Jihye Kim, Michael Katzman: Nothing to disclose.