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Emergence of Daptomycin-Resistant VRE: Experience of a Single Institution

Mini Kamboj, MD¹, Nina Cohen, PharmD¹, Kathleen Gilhuley, BS², N. Esther Babady, PhD², Susan K. Seo, MD¹, and Kent A. Sepkowitz, MD¹

¹Infectious Disease Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10065

²Microbiology Service, Department of Clinical Laboratories, Memorial Sloan-Kettering Cancer Center, New York, New York 10065.

Abstract

Recent surveillance from US hospitals shows that more than 99.5% of vancomycin-resistant enterococci (VRE) isolates remain susceptible to daptomycin. This report describes emergence of daptomycin-resistant VRE at a major cancer center. The percentage of patients with daptomycin-resistant VRE bacteremia increased from 3.4% in 2007 to 15.2% in 2009 ($P = .03$). Without susceptibility data, empiric daptomycin therapy for VRE infections should be used with caution.

Vancomycin-resistant enterococci (VRE) were first isolated in the United States in the late 1980s and have spread widely in the ensuing years. The most recent National Nosocomial Infection Surveillance (NNIS) report showed that 28.5% of all enterococcal isolates are resistant to vancomycin.¹ Studies have shown poorer clinical outcomes among patients with VRE infections when compared with those infected with vancomycin-susceptible enterococci.²

In the past decade, 4 new drugs with activity against VRE have been licensed for use: quinupristin-dalfopristin (1999), linezolid (2000), tigecycline (2005), and daptomycin (2003). Few studies have examined and compared the efficacy of these agents for use in the treatment of VRE infections. Among the newer drugs, common adverse effects such as myelotoxicity (linezolid) and myalgias (quinupristin-dalfopristin) limit the use in certain circumstances, especially among patients undergoing treatment for cancer.

Recent surveillance studies from US hospitals have demonstrated that more than 99.5% of VRE isolates remain susceptible to daptomycin.³ The purpose of this report is to describe the recent emergence at our hospital of daptomycin-resistant VRE strains.

METHODS

We examined the daptomycin susceptibility profile of all isolates collected during episodes of VRE bacteremia at Memorial Sloan-Kettering Cancer Center (MSKCC) from January 1, 2007, through December 31, 2009.

MSKCC is a 465-bed cancer center in New York City. Routine VRE surveillance is performed in the transplant and intensive care units. Information on all persons colonized or infected with VRE was obtained from the infection control database. Data on the use of daptomycin were obtained from the institutional pharmacy database. Clinical information was retrieved from electronic medical records. The MSKCC Institutional Review Board reviewed the study and granted a Health Insurance Portability and Accountability Act waiver of authorization.

Laboratory methods

Routine daptomycin susceptibility testing of *Enterococcus* isolates at MSKCC began in 2007 and was performed according to recommendations of the Clinical and Laboratory Standards Institute (CLSI).⁴ Susceptibility testing is performed using Microscan Gram-Positive Dried Panel 26 and read on autoSCAN-4 instruments (Siemens). Daptomycin dilutions in the panel ranged from 0.25 to 4 $\mu\text{g/mL}$ and included the CLSI-recommended calcium supplementation. CLSI recommends that any isolates for which the minimum inhibitory concentration (MIC) is greater than 4 $\mu\text{g/mL}$ be considered nonsusceptible. In this report, a daptomycin-resistant VRE is defined as an isolate with an MIC of greater than 4 $\mu\text{g/mL}$. Additional testing was conducted at Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, using the broth microdilution method (cation-adjusted Mueller-Hinton broth). Pulsed-field gel electrophoresis (PFGE) was performed after *SmaI* digestion and interpreted according to criteria previously described.⁵

Statistical analysis

Poisson regression was used to perform time-trend analysis on VRE healthcare-associated infection (HAI) rates from 2005 through 2009. The proportion of isolates resistant to daptomycin was analyzed using the Cochran-Armitage test for linear trend. A *P* value .05 was considered statistically significant. All analyses were performed using SAS, version 9.1 (SAS Institute).

RESULTS

From 2005 through 2009, VRE HAI rates did not change significantly at MSKCC: 0.79 cases per 1,000 patient-days in 2005 and 0.84 cases per 1,000 patient-days in 2009 (*P* = .44). No VRE outbreaks were identified. Daptomycin use (measured in doses) increased almost 4-fold during the 5-year interval (Figure 1).

From 2007 through 2009, 176 patients had VRE bacteremia at MSKCC, including 18 (10.2%) with bacteremia due to daptomycin-resistant VRE. All resistant strains were *Enterococcus faecium*. Overall at MSKCC, 95% of all VRE isolates are *E. faecium*. The percentage of patients with bacteremia due to a daptomycin-resistant VRE strain increased significantly, from 3.4% (2 of 58) in 2007 to 15.2% (10 of 66) in 2009 (*P* = .03) (Figure 1).

Of 18 patients with daptomycin-resistant VRE bacteremia, 15 (83%) had underlying hematologic malignancy (Table 1), 16 (89%) had no prior exposure to daptomycin, and 2 patients had received daptomycin for 5 and 17 days before the diagnostic culture sample was obtained. Of the 18 patients, 11 (61%) had mixed bacteremia, with isolation of daptomycin-susceptible and daptomycin-resistant strains during the same episode. Of these, only 1 had received daptomycin before or during the VRE bacteremia episode.

Isolates from 14 of the 18 patients with daptomycin-resistant VRE bacteremia were available for additional testing by the CDC; all 14 isolates had a daptomycin MIC in the resistant range (8 $\mu\text{g/mL}$ or greater), concordant with susceptibility testing performed at MSKCC.

Seven PFGE patterns were found among the 14 isolates. One common clone was isolated from 7 patients; however, these patients were not linked to each other in time or space. Serial VRE isolates from the same patient that showed different susceptibility to daptomycin demonstrated a clonal pattern by PFGE.

DISCUSSION

Daptomycin is a lipopeptide antibiotic that was first licensed for use in the United States in 2003. Daptomycin has bactericidal activity against methicillin-resistant *Staphylococcus aureus* and VRE and is currently approved for complicated skin and soft-tissue infections caused by certain gram-positive organisms, including *Enterococcus faecalis* (vancomycin-susceptible isolates only).

Data on the efficacy of daptomycin in treatment of infections due to VRE are limited. Despite this, daptomycin is often used to treat serious VRE infections because of limited antibiotic options, less frequent administration, fewer side effects, less potential for drug-drug interactions, and in vitro bactericidal activity against VRE.

Premarketing and surveillance studies⁶ have suggested that daptomycin resistance among VRE isolates is rare. The mechanism of resistance has not been completely elucidated, and mobile genetic elements that confer resistance have not been identified.⁷ A few reports of de novo resistance to daptomycin^{8,9} and that occurring during treatment^{10,11} have emerged in recent years. However, postmarketing surveillance of VRE isolates collected from US medical centers from 2007 through 2008 showed that 99.5% of *E. faecium* and 100% of *E. faecalis* isolates remain susceptible to daptomycin.³

Our study has several important findings. First, we have reported a statistically significant increase in daptomycin-resistant VRE isolates despite variable use of the drug during the study years. In 2009, 15% of patients with VRE bacteremia and VRE isolated from other clinical samples (Figure 1) demonstrated resistance to daptomycin, much higher than recent surveillance reports from US centers.³

Second, the majority of patients (89%) with bacteremia due to daptomycin-resistant VRE strains had no prior exposure to daptomycin and did not receive daptomycin for treatment of VRE bacteremia. Nosocomial transmission is certainly a possibility, although we did not find any epidemiologic link between these patients. Seven of 14 blood isolates that were typed by PFGE showed a common clone, which is endemic among VRE isolates at MSKCC.

Third, 61% of patients with daptomycin-resistant VRE bacteremia (Table 1) had mixed infection that included both resistant and susceptible strains, a finding that has important implications for management of these infections and emergence of resistance during treatment.

Our study has several limitations. We confirmed the results of our susceptibility testing with the CLSI broth microdilution method on blood isolates only. However, the proportion of daptomycin resistant VRE in blood and isolates from all sites was roughly the same, suggesting this is unlikely to change our findings. Second, we might have had an undiscerned outbreak of daptomycin resistant VRE. However patients sharing a common strain were not linked in time or space; furthermore the common strain of VRE isolated from seven patients is common in our hospital and was present long before acquiring the resistant phenotype.

In conclusion, resistance to daptomycin among VRE isolates is steadily emerging among patients with cancer at our hospital and may occur without prior daptomycin exposure. Susceptibility to daptomycin should be routinely evaluated for all VRE isolates, and empiric daptomycin therapy for VRE infections without the availability of susceptibility data should be used with caution.

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FIGURE 1.

Daptomycin use (shown with bars on left axis) and percentage of patients with daptomycin-resistant vancomycin-resistant enterococci (VRE) infections (represented by dotted and solid lines on right axis).

TABLE 1

Clinical Characteristics of 18 Patients with Bloodstream Infections due to Daptomycin-Resistant Vancomycin-Resistant Enterococci (VRE) at Memorial Sloan-Kettering Cancer Center (2007—2009)

Year, patient no.	Age, sex	Underlying cancer	Duration of prior exposure, days		Treatment	30-day mortality	Duration of bacteremia, days	Isolate resistance profile
			DAP	VANC				
2009								
1	71, F	Breast	0	90	None	Yes	1	DAP resistant only
2	6, F	NB	5	16	DAP	No	10	Mixed with DAP susceptible
3	55, M	AML	0	134	LZD	Yes	1	DAP resistant only
4	80, F	Ovarian	0	2	LZD	Yes	4	Mixed with DAP susceptible
5	58, F	CLL	0	20	LZD	No	2	DAP resistant only
6	66, F	Lymphoma	0	0	LZD	No	1	DAP resistant only
7	79, M	Lung	0	0	LZD	Yes	1	DAP resistant only
8	57, F	ALL-DUCBT	0	13	DAP gent	Yes	18	LZD and DAP resistant
9	32, M	ALL-DUCBT	0	31	DAP, LZD	No	9	Mixed with DAP susceptible
10	68, M	AML-PBSCT	0	37	LZD	No	7	Mixed with DAP susceptible
2008								
11	25, M	AML	0	2	LZD	Yes	15	Mixed with DAP susceptible
12	61, F	MDS/AML	0	47	LZD	No	1	Mixed with DAP susceptible
13	60, F	Lymphoma	0	26	LZD	No	1	DAP resistant only
14	65, F	MDS/PBSCT	0	15	LZD	No	3	Mixed with DAP susceptible
15	68, M	Lymphoma/PBSCT	0	1	LZD	No	2	Mixed with DAP susceptible
16	26, M	ALL/PBSCT	0	49	LZD	No	4	Mixed with DAP susceptible
2007								
17	64, M	AML	17	39	LZD	Yes	5	DAP resistant only
18	72, M	AML	0	19	LZD	No	1	Mixed with DAP susceptible

NOTE. ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; DAP, daptomycin; DUCBT, double umbilical cord blood transplant; gent, gentamicin; LZD, linezolid; MDS, myelodysplastic syndrome; NB, neuroblastoma; PBSCT, peripheral blood stem cell transplant; VANC, vancomycin.