CONCISE COMMUNICATION

Epidemiology of Vancomycin-Resistant Enterococci with Reduced Susceptibility to Daptomycin

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A retrospective case–case control study was conducted, including 60 cases with daptomycin-nonsusceptible vancomycin-resistant enterococci (DNS-VRE) matched to cases with daptomycin-susceptible VRE and to uninfected controls (1 : 1 : 3 ratio). Immunosuppression, presence of comorbid conditions, and prior exposure to antimicrobials were independent predictors of DNS-VRE, although prior daptomycin exposure occurred rarely. In summary, a case–case control study identified independent risk factors for the isolation of DNS-VRE: immunosuppression, multiple comorbid conditions, and prior exposures to cephalosporines and metronidazole.

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Daptomycin is one of only a few antimicrobials that has reliable bactericidal activity against vancomycin-resistant enterococci (VRE).[1] Although daptomycin nonsusceptibility (DNS) among clinical isolates of enterococci has been reported,[2] the epidemiology of DNS-VRE has not been systematically evaluated. This article describes a case–case control analysis that identified risk factors specifically associated with isolation of DNS-VRE.

METHODS

Detroit Medical Center (DMC) consists of 8 hospitals and has more than 2,200 inpatient beds. Institutional review boards at Wayne State University and DMC approved the study. Patients with clinical isolation of DNS-VRE from January 1, 2008, to December 31, 2009, were matched to two groups of patients in a 1 : 1 : 3 ratio: the first, patients with clinical isolation of daptomycin-susceptible (DS)-VRE; and the second, uninfected controls who did not have clinical isolation of enterococci. Matching parameters included (1) species of VRE, (2) anatomic site of the isolation of VRE, (3) facility, (4) unit, (5) calendar year, and (6) time at risk (ie, time from admission to culture for patients with VRE, and the total duration of hospital stay for uninfected controls). Time at risk had to be at least as long as the time at risk of their matched case. Once an eligible pool of controls was identified, controls were randomly selected using the randomization function in Excel (Microsoft). Active surveillance screening cultures were not performed routinely during the study period. Only the first episode of DNS-VRE isolation was analyzed for each patient.

Parameters retrieved from patient records included (1) demographics, (2) background conditions and comorbid conditions,[3] (3) recent healthcare-associated exposures, (4) previous antimicrobial exposures within the past 90 days, and (5) outcomes (including in hospital mortality, 3-month mortality, functional status deterioration, and total duration of hospital stay). Functional status and comorbidities were determined according to the documentation in charts, which was manually reviewed by trained physicians. The functional status was measured by reviewing the fall risk assessment filled out daily by the nurses. If the patient could ambulate without assistance, than the functional status was recorded as independent.

Bacteria at the DMC Clinical Microbiology Laboratory are analyzed using an automated broth microdilution system (MicroScan; Siemens) including the Prompt inoculation system (using the calcium supplementation recommended by the Clinical and Laboratory Standard Institutions [CLSI]). DNS was defined as daptomycin minimum inhibitory concentration (MIC) > 4 mg/L according to the CLSI criteria.[4]

All analyses were performed using IBM SPSS 19 (2011) and SAS software, version 9.2 (SAS Institute). Matched bivariate analyses were conducted using conditional logistic regression model. Continuous variables were examined by use of the nonparametric Wilcoxon test. Matched multivariable models were constructed using Cox proportional hazards regression, accounting for clustering on matched pairs. All variables with a P value of less than .1 in the bivariate matched analyses were considered for inclusion in the multivariate matched analyses. If a covariate affected the β-coefficient of a variable in the final model by more than 10%, then the confounding variable was maintained in the multivariable model. A 2-sided P value of less than .05 was considered statistically significant.

RESULTS

Sixty cases of DNS-VRE (56 *Enterococcus faecium*, 3 *Enterococcus faecalis*, and 1 nonspeciated *Enterococcus*) were identified, including 39 from urine, 15 from wounds, and 6 from blood. Sixty cases of DS-VRE and 175 uninfected controls were matched to DNS-VRE cases. For 2 DNS-VRE cases, only

1 matched uninfected control was identified; for 1 DNS-VRE case, only 2 matched uninfected controls were included. The overall mean age of the study cohort ($n = 295$) was 60.2 ± 18.2 years, 130 (44.1%) were male, 188 (64.8%) were black, and 81 (27.7%) were admitted from a long-term care facility or had been transferred from another hospital.

Bivariate analysis comparing DNS-VRE and uninfected controls, and DS-VRE and uninfected controls are displayed in Table 1. Exposure to daptomycin in the 3 months prior to admission was uncommon.

In multivariate analyses (Table 2), independent predictors for the isolation of DNS-VRE as compared to uninfected controls were a high Charlson weighted index comorbidity score (equal to 2 or more), presence of indwelling devices at the time of the VRE isolation, exposure to cephalosporins and/or metronidazole in the 3 months prior to hospital admission, and immunosuppressive status upon admission. Independent predictors for isolation of DS-VRE compared to uninfected controls included indwelling devices present at the time of VRE isolation, and exposure to cephalosporins or metronidazole or vancomycin in the 3 months prior to admission. When comparing the 2 models, immunosuppressive status and high Charlson score were uniquely associated with recovery of DNS-VRE. Presence of indwelling devices was strongly associated with isolation of DNS-VRE to a greater degree than DS-VRE.

No significant differences were noted between cases and controls in terms of in-hospital mortality and 3-month mortality (Table 1). Patients with VRE (either DNS-VRE or DS-VRE) more frequently experienced functional deterioration than uninfected controls. There was a trend towards increased functional deterioration among patients with DNS-VRE compared to DS-VRE ($P = .12$). Patients with VRE had longer total duration of hospitalization (length of stay [LOS]) compared to uninfected controls, and LOS was similar among patients with DNS-VRE and patients with DS-VRE ($P = .7$).

Fifty-six (93.3%) isolates were resistant to ampicillin in both the DNS-VRE and DS-VRE groups; 3 (5.0%) DNS-VRE strains and 1 (1.7%) DS-VRE isolates were resistant to linezolid; 10 (16.9%) DNS-VRE, and 9 (15.0%) DS-VRE strains demonstrated high-level resistance to gentamicin (MIC ≥500 mg/L); and 33 (55.9%) DNS-VRE and 44 (73.3%) DS-VRE isolated demonstrated high-level resistance to streptomycin (MIC ≥2000 mg/L).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the epidemiology of daptomycin nonsusceptibility among VRE isolates using strict epidemiologic criteria. Several important risk factors for isolation of DNS-VRE were identified.

Immunosuppression and having a high degree of chronic comorbid conditions were uniquely associated with isolation of DNS-VRE. Emergence of DNS-VRE among immunosuppressed patients with high degrees of chronic illness has been reported in the past.[5] Although indwelling devices (hazard ratio [HR]: 36.89 vs 3.35) and metronidazole exposure (HR: 44.81 vs 13.05) were associated with both DNS-VRE and DS-VRE, they were more strongly associated with DNS-VRE isolation than DS-VRE. Biofilm formation on a prosthetic device might provide suitable conditions for the development of mutations leading to decreased daptomycin susceptibilities.[6] Interestingly, daptomycin exposure was not identified as a risk factor for isolation of DNS-VRE in this study. Previous reports also documented the isolation of DNS-VRE among patients without prior daptomycin exposure.[2,5]

DNS-VRE isolates did not cluster in any single hospital location or in any particular time period during the study period. Daptomycin use began in 2006 at our medical center, and its use increased during the study period (mean DDD [defined daily doses] from 2008 to 2009: 7,322) compared to the prestudy period (mean DDD from 2006 to 2007: 2,611), although the trend of increase did not reach statistical significance. Although daptomycin exposure was not identified as a risk factor for isolation of DNS-VRE in this study, the increased use of daptomycin at the population level might have contributed DNS-VRE prevalence in our facility.

One limitation of the study is that study isolates were not available for typing or molecular analysis, so the mechanisms of daptomycin nonsusceptibility in the study cohort are unknown, although others have recently published on this topic.[7] Another limitation was that daptomycin nonsusceptibility was based on Microscan results, which defined resistant as MIC greater than 4. Possible discrepancies between daptomycin susceptibility results by MicroScan Panel and by Etest or CLSI broth microdilution methods for enterococci have been reported.[8,9] However, it remains unclear whether Etest or broth microdilution is more accurate or clinically significant. Although the presence of some inaccurate MIC test results might have been included in the study, data suggest that discrepancies are usually only 1–2 dilutions.[9] Thus, even in cases where a case of DNS-VRE might actually have been in a range categorized as susceptible to daptomycin, the MICs were likely close to the susceptibility breakpoint. Thus, we believe that the results of this study identify unique characteristics associated with elevated MICs to daptomycin. An additional limitation is that only 1 DS-VRE control was selected for each case of DNS-VRE due to the difficulty of identifying additional controls who met matching criteria.

DNS-VRE affects patients with severe comorbid conditions and extensive healthcare exposures. In order to limit the emergence and spread of DNS-VRE and to preserve daptomycin as a viable option for the treatment of gram-positive pathogens, strict infection control measures and appropriate antimicrobial stewardship practices are warranted when caring for patients who are at increased risk for DNS-VRE. Further explorations to determine the mechanisms of daptomycin resistance among enterococci are needed.

TABLE 1. Bivariate Analysis of Risk Factors and Outcomes for Isolation of Daptomycin-Nonsusceptible (DNS) and Daptomycin-Susceptible (DS) Vancomycin-Resistant *Enterococcus* (VRE), Detroit Medical Center, 2008–2009

	DNS-VRE cases	DS-VRE cases	Uninfected controls[a]	DNS-VRE vs uninfected controls		DS-VRE vs uninfected controls	
Variables	(n = 60)	(n = 60)	(n = 175)	OR (95% CI)	P value	OR (95% CI)	P value
Demographics							
Age, mean years (SD)	59.7 (15.9)	62.3 (18.0)	59.7 (19.1)		.997		.361
Male sex	25 (41.7)	21 (35.0)	84 (48.0)	0.75 (0.41–1.39)	.359	0.55 (0.29–1.04)	.068
Black	39 (65.0)	40 (70.2)	109 (63.0)	1.09 (0.51–2.31)	.824	1.40 (0.63–3.10)	.405
Non-home residence	15 (25.4)	17 (28.3)	49 (28.3)	0.88 (0.45–1.73)	.713	0.98 (0.51–1.90)	.955
Acute and chronic conditions on admission							
Dependent functional status	27 (45.8)	37 (62.7)	63 (37.5)	1.46 (0.78–2.73)	.239	2.87 (1.53–5.41)	.001
Impaired consciousness	18 (30.5)	25 (42.4)	38 (22.6)	1.90 (0.87–4.12)	.106	3.19 (1.54–6.62)	.002
Rapidly fatal McCabe score	6 (10.3)	3 (5.5)	18 (10.8)	0.94 (0.35–2.54)	.900	0.43 (0.12–1.57)	.199
Diabetes mellitus	24 (40.7)	22 (36.7)	47 (27.6)	1.95 (1.01–3.77)	.046	1.54 (0.81–2.92)	.189
Dementia	18 (30.5)	10 (16.7)	15 (8.9)	5.47 (2.23–13.42)	<.001	1.87 (0.81–4.34)	.145
Chronic skin ulcer	17 (28.8)	16 (26.7)	14 (8.3)	4.61 (2.02–10.50)	<.001	3.87 (1.73–8.66)	.001
Any liver disease	14 (23.7)	18 (30.0)	23 (13.6)	2.47 (1.07–5.72)	.035	3.75 (1.62–8.67)	.002
Any renal disease	20 (33.9)	28 (46.7)	48 (28.2)	1.55 (0.71–3.41)	.274	2.58 (1.32–5.01)	.005
Active malignant disease	11 (18.6)	16 (26.7)	21 (12.4)	2.04 (0.78–5.33)	.147	2.56 (1.23–5.33)	.014
Immunosuppressive state[b]	21 (35.6)	16 (26.7)	32 (18.7)	3.57 (1.53–8.34)	.003	1.58 (0.79–3.15)	.2
Charlson weighted index comorbidity, median (IQR)	3.6 (2.1–5.9)	3.4 (2.0–6.3)	2.1 (0.7–4.2)		<.001		.001
Charlson weighted index comorbidity (≥2)	52 (88.1)	50 (84.7)	100 (59.2)	8.05 (3.02–21.48)	<.001	5.77 (2.31–14.45)	<.001
Exposure to healthcare settings and environments before VRE isolation[c]							
Chronic hemodialysis	10 (16.9)	8 (13.3)	19 (10.9)	2.13 (0.76–5.99)	.151	1.32 (0.53–3.28)	.548
Indwelling devices[d]	41 (70.7)	36 (61)	45 (26.3)	13.34 (5.14–34.61)	<.001	5.44 (2.61–11.33)	<.001
Hospitalized in the past 3 months	35 (59.3)	43 (71.7)	99 (58.6)	1.07 (0.57–2.01)	.831	1.70 (0.90–3.20)	.102
Surgery or invasive procedure in the past 6 months	41 (69.5)	39 (65.0)	62 (36.5)	3.45 (1.86–6.42)	<.001	2.98 (1.60–5.54)	.001
ICU stay in the past 3 months	16 (27.6)	14 (23.7)	20 (11.7)	3.40 (1.44–8.02)	.005	3.87 (1.49–10.04)	.005

Antimicrobial exposure within 3 months before VRE isolation[c]							
Any antibiotics	46 (79.3)	50 (86.2)	45 (27.4)	9.96 (4.39–22.62)	<.001	23.79 (7.30–77.56)	<.001
Penicillins[e]	11 (19.6)	14 (24.1)	7 (4.2)	5.48 (1.88–15.06)	.002	10.22 (2.88–36.23)	<.001
Cephalosporins	31 (55.4)	32 (55.2)	23 (13.9)	7.99 (3.60–17.72)	<.001	8.29 (3.73–18.39)	<.001
Carbapenem	5 (8.9)	1 (1.7)	4 (2.4)	5.90 (1.12–30.98)	.036	0.72 (0.07–7.36)	.782
Vancomycin	20 (35.7)	28 (48.3)	16 (9.7)	4.89 (2.19–10.92)	<.001	10.38 (4.24–25.43)	<.001
Daptomycin	1 (1.8)	0	1 (0.6)	3.00 (0.19–47.96)	.437		.564
Linezolid	1 (1.8)	0	3 (1.8)	1.00 (0.10–9.61)	1		.992
Fluoroquinolone	14 (25)	16 (27.6)	9 (5.5)	6.70 (2.38–18.87)	<.001	5.13 (2.18–12.08)	<.001
Trimethoprim/sulfamethoxazole	1 (1.8)	5 (8.6)	3 (1.8)	1.30 (0.12–14.51)	.830	4.54 (1.08–19.08)	.039
Metronidazole	9 (16.1)	12 (20.7)	2 (1.2)	13.50(2.92–62.48)	.001	15.73 (3.50–70.67)	<.001
Clindamycin	3 (5.4)	6 (10.3)	7 (4.2)	0.92 (0.23–3.67)	.908	1.98 (0.65–6.01)	.229
Macrolide	4 (7.1)	5 (8.6)	1 (0.6)	10.18 (1.11–93.02)	.040	12.29 (1.41–106.94)	.023
Aminoglycosides	7 (12.5)	10 (17.2)	2 (1.2)	17.31 (2.11–142.02)	.008	25.22 (3.20–198.76)	.002
Tetracyclines	8 (14.3)	1 (1.7)	4 (2.4)	6.03 (1.56–23.29)	.009	0.54 (0.05–5.47)	.598
Outcomes							
In-hospital mortality	7 (11.7)	7 (11.7)	26 (15.1)	0.58 (0.20–1.68)	.311	0.62 (0.23–1.69)	.346
3-month mortality[f]	5 (11.1)	4 (8.5)	6 (4.5)	1.54 (0.37–6.48)	.557	1.45 (0.31–6.73)	.636
Functional status deterioration	14 (27.5)	6 (11.8)	5 (3.6)	11.97 (2.61–54.89)	.001	3.07 (0.81–11.64)	.099
Total LOS, median days (IQR)	9 (6.3–21.8)	10.5 (6–24.8)	7 (3–17)		.005		.003

NOTE. The percentage is of patients for whom data were available, ie, excluding the missing cases. Values are no. (%) unless otherwise indicated. CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; OR, odds ratio; SD, standard deviation.

[a] For 2 DNS-VRE cases, only 1 matched uninfected control was found; for 1 DNS-VRE case, only 2 matched uninfected controls were found.

[b] Includes 1 or more of the following: (1) neutropenia (<500 neutrophils) at time of culture, (2) glucocorticoid/steroid use in the past month, (3) chemotherapy in the past 3 months, (4) radiotherapy in the past 3 months, (5) posttransplantation, or (6) anti-tumor necrosis factor α (TNF-α) therapy in the past 3 months.

[c] For uninfected controls, prior to admission.

[d] Indwelling devices (eg, tracheotomies, central lines, urinary catheters, orthopedic external fixators) that were in place at least 48 hours prior to VRE isolation. For uninfected controls, indwelling devices that were in place at admission.

[e] Penicillins include β-lactam/β-lactamase inhibitor combinations.

[f] The 3-month mortality was available on 45 (75%) of DNS-VRE, 47 (78%) of DS-VRE, and 134 (77%) of uninfected controls.

TABLE 2. Multivariate Analyses of Risk Factors for Isolation of Daptomycin-Nonsusceptible (DNS) and Daptomycin-Susceptible (DS) Vancomycin-Resistant *Enterococcus* (VRE)

	DNS-VRE vs uninfected controls		DS-VRE vs uninfected controls	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Charlson weighted index comorbidity (≥2)	14.16 (2.22–90.24)	.005	1.61 (0.46–5.64)	.46
Indwelling devices[a] at VRE isolation	36.89 (5.37–253.26)	<.001	3.35 (1.10–10.20)	.033
Surgery or invasive procedures in the past 6 months	1.47 (0.45–4.85)	.523	1.11 (0.41–2.99)	.844
ICU stay in the past 3 months	0.83 (0.16–4.42)	.828	0.81 (0.14–4.61)	.813
Cephalosporins in the past 3 months	4.14 (1.04–16.53)	.045	4.14 (1.33–12.95)	.014
Fluoroquinolones in the past 3 months	3.24 (0.63–16.75)	.161	3.40 (0.85–13.63)	.085
Metronidazole in the past 3 months	44.81 (3.21–625.87)	.005	13.05 (1.95–87.23)	.008
Vancomycin in the past 3 months	1.50 (0.38–5.96)	.563	5.18 (1.54–17.43)	.008
Immunosuppressive status on admission	13.53 (2.19–83.62)	.005		
Impaired consciousness on admission			2.10 (0.64–6.91)	.221

NOTE. CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

[a] Indwelling devices (eg, tracheotomies, central lines, urinary catheters, orthopedic external fixators) that were in place at least 48 hours prior to VRE isolation. For uninfected controls, indwelling devices that were in place at admission.

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