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Evaluation of Risk Factors for Coinfection or Cocolonization with Vancomycin-Resistant Enterococcus and Methicillin-Resistant *Staphylococcus aureus*▽

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We retrospectively evaluated 410 patients with coinfection or cocolonization due to vancomycin-resistant (VR) enterococcus (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). The prevalence rate was 19.8%. Risk factors included isolation of VR *Enterococcus faecalis* and use of linezolid or clindamycin. Inc18-like *vanA* plasmids were found in 7% of VR *E. faecalis* isolates and none of the VR *E. faecium* isolates.

The emergence of vancomycin resistance in *Staphylococcus aureus*, with 7 of 9 cases worldwide from southeast Michigan (12, 13), is alarming. The isolation of enterococci containing the *vanA* gene identical to those of vancomycin-resistant (VR) *S. aureus* (VRSA) strains suggests that the *vanA*-mediated resistance was due to the transfer of an Inc18-type plasmid from VRE containing *traA* and *repR* genes to *S. aureus* (3, 5). Accordingly, isolation of both VRE and methicillin-resistant *S. aureus* (MRSA) may be one of the foremost risk factors for the development of VRSA. The National Healthcare Safety Network report for 2006–2007 identified VRE and MRSA as the two most common antimicrobial-resistant pathogens associated with health care-associated infections (8). Our study aimed to evaluate risk factors and epidemiology of colonization or infection with both VRE and MRSA. We also investigated the occurrence of *traA* and *repR* genes among VRE isolates to gain information on its potential role as a resistance mechanism for VRSA.

Microbiology records from a 900-bed tertiary-care facility in urban Detroit, MI, from January 2005 through December 2007 were reviewed for data from patients who had at least one culture positive for VRE. Cocolonization or coinfection with MRSA was defined as the isolation of at least one culture positive for MRSA within 14 days from the date of VRE isolation. Data from October to December 2007 included MRSA surveillance cultures. *In vitro* susceptibilities were determined by the clinical microbiology laboratory (4). PCR analysis was performed to detect the presence of *traA* and *repR* genes among VRE isolates (17). Through retrospective chart review, clinical patient characteristics were collected. Statistical comparisons employed *t* tests, Wilcoxon rank sum tests, and chi-square or Fisher exact tests where appropriate. Multivariate analysis used a stepwise logistic regression model.

Four hundred ten patients were identified to have VRE, 57 (13.9%) had VR *Enterococcus faecalis*, 272 (66.3%) had VR *E. faecium*, and 81 (19.8%) had both VRE and MRSA. Clinical characteristics of patients with VRE alone and patients cocolonized or coinfected with VRE and MRSA are shown in Table 1. Table 2 lists the sources of the isolates, with skin or wounds being more significantly common for patients with both VRE and MRSA than for patients with VRE alone. VR *E. faecalis* rather than VR *E. faecium* was most commonly associated with cocolonization or coinfection with MRSA (35% versus 17.3%). The independent risk factors for VRE-MRSA cocolonization or coinfection are shown in Table 3 and include isolation of VR *E. faecalis* and prior receipt of linezolid or clindamycin in the last 90 days. *traA* and *repR* genes were found in 4 (7.02%) of the 57 VR *E. faecalis* isolates, and these genes were not found among VR *E. faecium* isolates. The 4 VR *E. faecalis* isolates were taken from blood ($n = 2$), the urinary tract ($n = 1$), and a surgical site ($n = 1$).

In this study, VRE-MRSA cocolonization or coinfection was common, occurring in 20% of all patients studied. Prior studies on cocolonization or coinfection with VRE and MRSA (1, 6, 7, 9, 11, 15) demonstrated prevalence rates ranging from 2.7% to 28.6% (6, 7, 10, 15). We found the major risk factors for VRE and MRSA cocolonization or coinfection were isolation of VR *E. faecalis*, rather than *E. faecium*, and exposure to the antimicrobials linezolid and clindamycin. Earlier studies demonstrated different findings. Furuno et al. (7) showed age, admission to a medical intensive care unit, male gender, and receiving antimicrobial drugs on a previous admission within the preceding year as risk factors; Warren et al. (15) found age, hospitalization during the preceding 6 months, and admission to a long-term-care facility to be risks; and Polgreen et al. (11) reported residency in long-term-care facilities as a risk factor for both MRSA and VRE infections. Though vancomycin resistance was more common among *E. faecium* isolates, in this study, *E. faecalis* was independently associated with cocolonization or coinfection with MRSA. This finding has an important implication in a potential role of the organism in relation to VRSA isolation (3, 10). The reason for linezolid and clindamycin being major risk factors is unclear and was not determined by the study. Both antimicrobial agents have anti-

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TABLE 1. Clinical characteristics of patients with VRE and patients with both VRE and MRSA

Variable[a]	Patients with VRE (n = 329)	Patients with VRE and MRSA (n = 81)	P value[b]
Mean ± SD			
Age (yr)	63.2 ± 16.5	64.5 ± 15.1	0.511
Length of stay in hospital (days)	23.7 ± 29.1	26.7 ± 34.3	0.267
No. (%) of patients			
Male	141 (42.9)	39 (48.1)	0.390
Prior hospitalization	264 (80.2)	60 (75.0)	0.300
Prior ICU stay	72 (21.9)	21 (26.6)	0.371
Prior surgery	147 (44.8)	23 (28.8)	0.009*
Nursing home stay	78 (23.8)	24 (30.0)	0.249
Wound care clinic visits	12 (3.7)	2 (2.5)	1.000
Central venous catheter for >72 h	81 (24.6)	7 (8.8)	0.002*
Indwelling Foley catheter	24 (7.3)	6 (7.5)	0.950
Chronic wound or ulcer	89 (27.1)	15 (18.8)	0.123
Myocardial infarct	63 (19.1)	19 (23.8)	0.357
Congestive heart failure	69 (21.0)	18 (22.5)	0.765
Chronic obstructive pulmonary disease	41 (12.5)	16 (20)	0.085
Peripheral vascular disease	32 (9.8)	7 (8.8)	0.784
Cerebrovascular accident	51 (15.5)	11 (13.8)	0.695
Connective tissue disease	51 (15.5)	2 (2.5)	0.002*
Gastrointestinal ulcer bleeding	25 (7.6)	5 (6.3)	0.678
Dementia	35 (10.7)	6 (7.5)	0.394
Intravenous drug use	17 (5.2)	4 (5.0)	1.000
Chemotherapy	30 (9.2)	0 (0.0)	0.005*
Corticosteroids	14 (4.3)	1 (1.3)	0.322
HIV infection	6 (1.8)	0 (0.0)	0.603
Neutropenia	2 (0.6)	0 (0.0)	1.000
Leukemia	11 (3.4)	2 (2.5)	1.000
Solid tumor	75 (22.9)	11 (13.6)	0.066
Transplant recipient	29 (8.8)	4 (5.0)	0.261
Diabetes with end organ damage	45 (13.7)	0 (0.0)	<0.001*
Acute renal failure	32 (12.4)	13 (100.0)	<0.001*
Chronic kidney disease	107 (32.7)	19 (23.8)	0.120
Prior antibiotic use in last 90 days			
Vancomycin	123 (37.6)	31 (38.3)	0.913
Linezolid	12 (3.7)	7 (8.6)	0.074
Daptomycin	1 (0.3)	1 (1.2)	0.359
Trimethoprim-sulfamethoxazole	40 (12.2)	4 (4.9)	0.060
Tetracycline	5 (1.5)	0 (0.0)	0.588
Penicillins	19 (5.8)	4 (4.9)	1.000
Beta-lactams	71 (21.8)	8 (9.9)	0.015*
Cephalosporin	87 (26.7)	13 (16.0)	0.047*
Carbapenem	28 (8.6)	5 (6.2)	0.480
Metronidazole	37 (11.3)	4 (4.9)	0.087
Clindamycin	7 (2.2)	5 (6.2)	0.070
Fluoroquinolone	94 (28.7)	13 (16.0)	0.021*
Aminoglycoside	41 (12.6)	4 (4.9)	0.049*
No antibacterial use	46 (14.1)	30 (37.5)	<0.001*

[a] ICU, intensive care unit.
[b] *, significant value.

MRSA activity, and linezolid has *in vitro* activity against both enterococci and MRSA. Linezolid and clindamycin also inhibit protein synthesis and toxin production, which may have an impact on a virulence characteristic associated with colonization. With the recent rise in the use of linezolid, further studies are needed to determine a dynamic potential role in an interrelationship between VRE and MRSA. It remains a challenge to completely understand the relationship between the use of a specific agent and resistance and infections with resistant organisms. The Centers for Disease Control and Prevention advocate careful oversight of vancomycin use in the control of multidrug-resistant organisms (2). Given the results of this study, in geographic areas where VRE and MRSA are endemic, additional monitoring and control of the use of linezolid and clindamycin may be of importance.

Our study is unique in determining the incidence of *traA* and *repR* genes among VRE in a geographic area known to have VRSA. The *vanA* VRE plasmid from the first VRSA isolate was identified as an Inc18-like plasmid (5, 16, 17), which was related to the VRE *vanA* plasmids associated with the latter VRSA cases. The latter plasmids were characterized by the detection of the two Inc18-specific genes *traA* and *repR* (14, 17). This study shows that Inc18-like *vanA* plasmids are rare among vancomycin-resistant *E. faecalis* and *E. faecium* isolates.

TABLE 2. Infection sources of patients with VRE and patients with both VRE and MRSA

Variable	No. (%) of patients with:		*P* value[a]
	VRE (n = 329)	VRE and MRSA (n = 81)	
VR *E. faecalis* present	57 (17.3)	28 (35.0)	<0.001*
Source			
Catheter	37 (11.3)	0 (0.0)	0.001*
Endocarditis	3 (0.9)	0 (0.0)	1.000
Skin/wound	48 (14.6)	20 (24.7)	0.029*
Intra-abdominal	32 (9.8)	4 (4.9)	0.166
Respiratory	5 (1.5)	1 (1.2)	1.000
Urinary tract	163 (49.5)	42 (51.9)	0.710
Bacteremia	83 (25.3)	22 (27.2)	0.732
Undetermined	9 (2.8)	0 (0.0)	0.215

[a] *, significant value.

Importantly, all 4 *traA*- and *repR*-positive isolates are strains of VR *E. faecalis.* The four patients resided in southeast Michigan, with ages ranging from 38 to 83 years, had chronic illnesses like diabetes, osteomyelitis, and renal disease on hemodialysis. These are characteristics similar to the 7 Michigan VRSA cases. None of 4 patients was cocolonized or coinfected with MRSA, but 2 had remote *S. aureus* infections. The potential exchange of genetic information, especially the *vanA* gene, between and among staphylococci and enterococci remains a challenge concerning infection, prevention, and therapy (9, 12).

Limitations of our study include evaluation in a single hospital located in a metropolitan area. The VRE isolates examined for Inc18-like plasmids all originated in southeast Michigan. Limited data for the prevalence of *traA* and *repR* genes from other regions exist. VRE-MRSA coinfection or cocolonization was defined using a 14-day cutoff period, which could have missed subsequent MRSA cultures. As this is a retrospective study which used clinical cultures and surveillance MRSA cultures, we could have underestimated the true proportion of patients colonized with VRE and MRSA among selected patients.

Cocolonization or coinfection with VRE and MRSA was common in this study (20% prevalence). Independent risk factors include isolation of VR *E. faecalis* rather than *E. faecium* and prior use of linezolid or clindamycin. *traA* and *repR* genes, the roles of which remain unclear in the emergence of VRSA, are infrequent among VRE but were found in *E. faecalis* isolates. Patients who tested positive for the Inc18-like plasmids share similar characteristics with the VRSA cases. Infection prevention interventions for vancomycin-resistant *E. faecalis* may need particular attention.

TABLE 3. Independent predictors of cocolonization or coinfection with vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus*

Variable[a]	*P* value	Odds ratio	Odds ratio confidence	95% limit
Presence of VR *E. faecalis* vs VR *E. faecium*	<0.001	3.694	1.901	7.176
Linezolid	<0.001	8.981	2.673	30.175
Clindamycin	0.021	4.994	1.271	19.625
Metronidazole	0.034	0.242	0.065	0.901
No antibacterial use	<0.001	6.989	3.519	13.879
Connective tissue disease	0.020	0.171	0.039	0.757
CVC > 72 h	0.002	0.246	0.101	0.599

[a] CVC, central venous catheter.

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