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Prevalence and Risk Factors Associated with Vancomycin-Resistant *Staphylococcus aureus* Precursor Organism Colonization among Patients with Chronic Lower-Extremity Wounds in Southeastern Michigan

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Abstract

BACKGROUND—Of the 13 US vancomycin-resistant *Staphylococcus aureus* (VRSA) cases, 8 were identified in southeastern Michigan, primarily in patients with chronic lower-extremity

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wounds. VRSA infections develop when the *vanA* gene from vancomycin-resistant enterococcus (VRE) transfers to *S. aureus*. Inc18-like plasmids in VRE and pSK41-like plasmids in *S. aureus* appear to be important precursors to this transfer.

OBJECTIVE—Identify the prevalence of VRSA precursor organisms.

DESIGN—Prospective cohort with embedded case-control study.

PARTICIPANTS—Southeastern Michigan adults with chronic lower-extremity wounds.

METHODS—Adults presenting to 3 southeastern Michigan medical centers during the period February 15 through March 4, 2011, with chronic lower-extremity wounds had wound, nares, and perirectal swab specimens cultured for *S. aureus* and VRE, which were tested for pSK41-like and Inc18-like plasmids by polymerase chain reaction. We interviewed participants and reviewed clinical records. Risk factors for pSK41-positive *S. aureus* were assessed among all study participants (cohort analysis) and among only *S.* aureus-colonized participants (case-control analysis).

RESULTS—Of 179 participants with wound cultures, 26% were colonized with methicillinsusceptible *S. aureus*, 27% were colonized with methicillin-resistant *S. aureus*, and 4% were colonized with VRE, although only 17% consented to perirectal culture. Six participants (3%) had pSK41-positive *S. aureus*, and none had Inc18-positive VRE. Having chronic wounds for over 2 years was associated with pSK41-positive *S. aureus* colonization in both analyses.

CONCLUSIONS—Colonization with VRSA precursor organisms was rare. Having long-standing chronic wounds was a risk factor for pSK41-positive *S. aureus* colonization. Additional investigation into the prevalence of VRSA precursors among a larger cohort of patients is warranted.

Since its emergence in Detroit, Michigan, in 2002, vancomycin-resistant *Staphylococcus aureus* (VRSA) has been identified in 13 patients in the United States, including 8 patients from southeastern (SE) Michigan. These patients presented with similar comorbidities, including chronic lower-extremity wounds.

The development of vancomycin resistance among *S. aureus* appears to result from conjugation of vancomycin-resistant enterococcus (VRE) with *S. aureus* resulting in the exchange of the *vanA* operon, which confers vancomycin resistance.⁴ Although *Enterococcus faecium* is the most common species of VRE in the United States, enterococci other than *E. faecium* have been identified as *vanA* donors for VRSA cases in which a donor was identified.⁵ The exchange of *vanA* is suspected to be facilitated by specific plasmids, including Inc18-like donor plasmids in VRE and pSK41-like recipient plasmids in *S. aureus*^{5–8} The prevalence of Inc18-like plasmids in VRE appears to be higher in Michigan (3.9%) than in other states (0.7%).⁵

Current knowledge regarding the epidemiology of VRSA is limited to uncontrolled descriptions of the initial cases. ^{2,9–12} In addition, no evaluation of the prevalence of this organism and its precursors in high-risk populations have been reported other than limited evaluations of the contacts of the initial VRSA case-patients. The objective of this study was

to identify the proportion of patients with chronic lower-extremity wounds in SE Michigan colonized with Inc18-possitive VRE and/or pSK41-positive *S. aureus*.

METHODS

The study protocol was approved by the institutional review boards of the Centers for Disease Control and Prevention (CDC), the Michigan Department of Community Health, William Beaumont Hospital, Detroit Medical Center, and Henry Ford Health System. A convenience sample of adults 18 years of age or older with chronic lower-extremity wounds who presented to William Beaumont Hospital, Detroit Medical Center, or Henry Ford Hospital during the period February 15-March 4, 2011 were approached for enrollment. Participants were excluded if they were pregnant, incarcerated, had impaired decisional capacity without a legal guardian present, did not speak English, or did not live in SE Michigan. Written consent was obtained for participation in the study.

A survey was administered to each study participant querying demographic characteristics, wound information, antimicrobial history, and medical history. Antimicrobial history was corroborated through medical and outpatient pharmacy record review. Wound, perirectal, and nares swab samples were collected for culture; participants were permitted to decline perirectal or nares swabs.

Swabs were stored at 4°C and shipped weekly to the CDC for culture (nares swabs were cultured for *S. aureus*, and wound and perirectal swabs were cultured for *S. aureus* and VRE). Swab specimens were incubated overnight in Trypti-case soy broth (TSB) with 6.5% NaCl at 35°C and then plated onto CHROMagar *Staph aureus* (DRG International) and CHROMagar VRE plates (DRG International) for selection of *S. aureus* and VRE, respectively. Plates were examined after 24 and 48 hours incubation at 35°C. Morphologically distinct colonies were worked-up from each culture plate. Colony identity was confirmed using Staphaurex (Remel) for *S. aureus* and PYR disk for VRE (Hardy Diagnostics). Confirmed colonies were subcultured on tryptic soy agar with 5% sheep blood and stored frozen at –70°C in TSB with 15% glycerol. Methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates were tested for pSK41-like plasmids by polymerase chain reaction (PCR) for *traE* and *repA* genes and VRE isolates were tested for Inc18-like plasmids by PCR for *traA* and *repA* genes. 5,6 *S. aureus* isolates positive for pSK41-like plasmids were typed by pulsed-field gel electrophoresis (PFGE) and *spa* typing. 13,14

Analysis

Descriptive analysis was performed to summarize the clinical characteristics and microbiologic results of study participants. Functional disability was defined as the inability to independently bathe, walk, cook, or dress for oneself. Charlson comorbidity index scores were calculated. For pSK41-positive staphylococci, the following risk factor analyses were conducted: (i) cohort analysis to determine the risk factors for carriage among all participants of the study, and (ii) embedded case-control analysis to determine risk factors for carriage among participants colonized with *S. aureus*.

Comparative analyses were performed using Fisher exact test; relative risks (RR) and odds ratios (OR) were calculated accordingly. Statistical significance was defined as P < .05. A correction factor of 0.5 per cell was used to estimate RRs and ORs for which the result would have otherwise been undefined. All statistical analyses were conducted using SAS 9.3 (SAS Institute).

RESULTS

Patient Characteristics

In total, 179 participants were enrolled in the study (41 from William Beaumont, 69 from Detroit Medical Center, and 69 from Henry Ford Health System). The demographic and clinical characteristics of study participants are summarized in Table 1.

Prevalence of S. aureus, VRE, and VRSA-Precursor Plasmids

The prevalence of *S. aureus* and VRE colonization among participants and cultures is summarized in Table 2. Of note, 35% of participants were colonized with MRSA in at least 1 site, and none of the 8 participants with wound cultures positive for VRE had perirectal swab samples obtained. None of the 12 VRE were identified as *E. faecium*; 5 were identified as *Enterococcus faecalis*, and 7 were ruled-out as *E. faecalis* or *E. faecium*. No Inc18 VRE were identified; the prevalence of pSK41 is shown in Table 2.

A total of 112 study participants (63%) were colonized with *S. aureus*; 50 (45%) were colonized with only MSSA, 56 (50%) were colonized with only MRSA and 7 (6%) were colonized with both MSSA and MRSA. Ten *S. aureus* isolates from 6 participants were pSK41 positive (Table 2): 3 were colonized with only pSK41-positive MRSA (total of 4 MRSA isolates), 1 was colonized with only pSK41-positive MSSA (total of 1 MSSA isolate), and 2 were colonized with both pSK41-positive MRSA and pSK41-positive MSSA (total of 2 MRSA isolates and 3 MSSA isolates). The clinical characteristics of the 6 participants colonized with pSK41-positive *S. aureus* are summarized in Table 3. None of these 6 participants were older than 65 years or employed, and only 1 (case 4) had any functional disability. No VRSA cases were identified in the study.

Strain and spa Typing of pSK41-Positive S. aureus Isolates

The 4 MSSA isolates and 6 MRSA isolates from the 6 participants colonized with pSK41-positive *S. aureus* were strain typed by PFGE. Of the 4 MSSA isolates, 1 was a USA300 clone, 2 were USA800 clones, and 1 had a nontypeable PFGE pattern. Of the 6 MRSA isolates, 1 was a USA100 clone, and 5 were USA300 clones. All 6 USA300 clones (5 MRSA and 1 MSSA) were *spa* type t008, both USA800 clones (both MSSA) and the USA100 clone (MRSA) were *spa* type t002,and the nontypeable clone (MSSA) was *spa* type t193. The USA800 and USA100 isolates were all recovered from a single patient and were closely related by PFGE analysis, with only the apparent loss of the band containing *mecA* resulting in the difference between USA800 and USA100 isolates (not shown). Likewise, the other patient colonized with pSK41-positive MRSA and MSSA was carrying 2 very closely related USA300 that differed only by the *mecA*-containing band (not shown).

Risk Factor Evaluation

Because Inc18-positive VRE was not identified, risk factor analyses to assess carriage of VRSA precursors were performed only for pSK41-positive S. aureus. In the cohort analysis of all study participants, having chronic wounds for over 2 years (potentially different, sequential wounds) was a significant risk factor for pSK41-positive S. aureus colonization (RR, 20.51; P= .004). Similarly, in the case-control analysis of participants colonized with S. aureus, having chronic wounds for over 2 years was significantly associated with pSK41-positive S. aureus colonization (OR, 20.52; P= .005). No other demographic and clinical variables were significantly associated with pSK41-positive S. aureus colonization, although there was a trend toward significance observed with receipt of trimethoprim-sulfamethoxazole (TMP-SMX) in the cohort analysis (RR, 4.11; P= .09) and case-control analysis (OR, 5.24; P= .07).

DISCUSSION

We enrolled participants with similar demographic characteristics and medical comorbidities as previously identified VRSA case-patients.^{2,17} A large proportion of participants were colonized with MRSA (35%); this proportion is higher than reported for other groups, including dialysis patients and elderly patients in long-term care facilities.¹⁸ The high prevalence of *S. aureus* and MRSA in this study population may be attributable to the high proportions of participants with significant medical comorbidities, antimicrobial exposure, and/or recent healthcare exposure compared with the general population. Furthermore, the frequency of *S. aureus* colonization in chronic wounds is known to be greater than in similar populations without open wounds.¹⁹

VRE colonization, however, was found in only 7% of study participants; none of these VRE isolates were Inc18 positive. The prevalence of VRE and Inc18-positive VRE in this patient population was likely underrepresented in our study because of the fact that only 31 participants (17%) consented to collection of a perirectal swab.

Although VRE screening was limited, we had a sufficient number of nares and wound swab samples to screen for *S. aureus* among all participants. We found only 6 participants (3%) were colonized with pSK41-positive *S. aureus*, which suggests that colonization with VRSA-precursor organisms is uncommon even among a patient population thought to be at higher risk of colonization. This finding is consistent with the rarity with which VRSA isolates have been identified. Interestingly, pSK41 plasmids were found in 5% of MSSA isolates, a proportion similar to that found in MRSA.

Strain-type analysis revealed that 4 of 6 patients colonized with pSK41-positive *S. aureus* were carrying USA300 clones (including 1 pSK41-positive MSSA isolate), whereas only 1 patient was colonized with *spa*-type t002 strains (USA100 and USA800), which are classified as clonal complex 5. Of the 13 VRSA cases reported to date, none were USA300, and 12 of 13 have been related to USA100 by multilocus sequence typing (clonal complex 5; CDC, unpublished data). Although all previous VRSA cases were associated with extensive health-care exposures, this study highlights that pSK41 recipient plasmids are present in multiple strains, including those associated with the community. This is not an uncommon

finding and has been previously described, which suggests that there is potential for VRSA to occur among community strains.⁶ In fact, the most recent VRSA case patient was carrying USA1100, a community *S. aureus* strain (CDC, unpublished data).

Our risk factor analyses found that having chronic wounds for over 2 years (potentially different, sequential wounds) was associated with pSK41-positive *S. aureus* colonization. This is consistent with the observation that many of the known VRSA cases had problems with chronic wounds. The reason for this association is not clear, but possible factors include a cumulative antimicrobial effect, changes in vascular flow, and the development of polymicrobial biofilms. ²⁰ The marginally significant association we observed with TMP-SMX exposure is not clearly understood but may be related to the potential for pSK41 plasmids to carry trimethoprim resistance gene *dfrA;* however, we were unable to assess for potential confounders, including other underlying comorbidities. Possible association with other risk factors (eg, diabetes and end-stage renal disease) could not be excluded, because this study was underpowered to detect such associations as the result of the small sample size.

There were several limitations to this study in addition to the small sample size and limited numbers of perirectal swab samples. Because *S. aureus*, VRE, and VRSA-precursor organism colonization was evaluated with a single swab per sample site at a single time point, there was a risk of mis-classification because of sampling error. Additionally, the enrollment of study participants was limited to a 3-week period, which may not have allowed sufficient time to capture a representative population of patients in SE Michigan with chronic wounds. However, this study was conducted across the wound clinics and emergency departments of 3 main medical centers, thus representing a large catchment area of SE Michigan. This study relied on data derived from participant self-report, which may have introduced misclassification bias; however, antimicrobial exposures were confirmed with medical and outpatient pharmacy records, which was a strength of this study. Finally, the focus of this study was on outpatients, primarily wound clinic patients, and most of the known VRSA cases had multiple healthcare encounters and prolonged healthcare exposures; therefore, the reservoir for the precursor organisms might be more common in other settings.

This was the first study to investigate the prevalence of VRSA-precursors among patients with chronic lower-extremity ulcers in SE Michigan. We found that colonization with pSK41-positive *S. aureus* was rare. Additional investigation into the prevalence of Inc18 and risk factors for VRSA-pre-cursor colonization among a larger cohort of patients is warranted.

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TABLE 1.

Baseline Characteristics of Study Participants with Chronic Lower-Extremity Wounds in Southeastern Michigan, 2011

	Participants
	57 (27–93)
	109 (61)
	70 (39)
	100 (57)
	72 (41)
Other/unknown/decline to state	4 (2)
Annual household income $(n = 172)$	
	57 (33)
	46 (27)
	69 (40)
	25 (14)
	154 (86)
	90 (52)
	82 (48)
	49 (27)
	130 (73)
	81 (45)
	47 (26)
	43 (24)
	37 (21)
History of myocardial infarction	28 (16)
	9 (5)

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Characteristic	Participants
Charlson comorbidity index score $(n = 179)$	
0	43 (24)
1-3	96 (54)
4-6	20 (11)
7–12	19 (11)
>12	1 (1)
Duration of chronic wounds (potentially different, sequential wounds; $n = 179$)	ounds; $n = 179$)
<3 months	33 (18)
3–6 months	30 (17)
>6 months to 12 months	23 (13)
>12 months to 2 years	20 (11)
>2 years	73 (41)
Indwelling devices in the previous 3 months $(n = 177)$	
Any	47 (26)
Central venous catheter	37 (21)
Other devices (eg, urinary catheter and PEG)	17 (10)
Healthcare exposure	
Ever hospitalized $(n = 178)$	161 (90)
2 hospitalizations in the previous 12 months ($n = 155$)	63 (41)
Hospitalized in the previous 3 months ($n = 177$)	61 (34)
Ever stay in a long-term care facility $(n = 177)$	43 (24)
Long-term care facility in the previous 3 months $(n = 160)$	15 (9)
Antimicrobials in the previous 3 months ($n = 179$)	
Any	122 (68)
Vancomycin	46 (26)
Daptomycin	2(1)
Linezolid	1 (1)
Penicillin	2(1)
eta-lactamase inhibitor combinations	16 (9)
Cephalosporin	45 (25)
Carbapenem	6 (3)

Characteristic	Participants
Aminoglycoside	1 (1)
Macrolide	5 (3)
Trimethoprim-sulfamethoxazole	35 (20)
Clindamycin	10 (6)
Tetracycline	3 (2)
Fluoroquinolone	33 (18)

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NOTE. Data are no. (%) of patients, unless otherwise indicated. PEG, percutaneous endoscopic gastrostomy.

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TABLE 2.

Swab Specimen Culture Results from Study Participants with Chronic Lower-Extremity Wounds in Southeastern Michigan, 2011

Culture site	No. of patients MSSA po	MSSA positive	ositive pSK41 MSSA positive MRSA positive pSK41 MRSA positive VRE positive	MRSA positive	pSK41 MRSA positive	VRE positive	MRSA and MSSA positive	Staphylococcus aureus and VRE positive
Any culture site Specific culture sites	179	57 (32)	3 (2)	62 (35)	5 (3)	12 (7)	7 (4) ^b	7 (4) ^C
Nares	177	35 (20)	2(1)	44 (25)	3 (2)	NA	0 (0)	0 (0)
Wound	179	46 (26)	1 (1)	49 (27)	2(1)	8 (4)	0 (0)	0 (0)
Perirectal	31	5 (16)	1 (3)	4 (13)	1 (3)	4 (13)	0 (0)	0 (0)

NOTE. Data are no. (%) of patients. MRSA, methicillin-resistant S. aureus, MSSA, methicillin-susceptible S. aureus, NA, not applicable; VRE, vancomycin-resistant enterococcus.

 $^{^{}a}$ Includes results of any site cultured for each patient; of note, not all patients had all sites cultured.

 $b_{\mbox{\footnotesize None}}$ were positive for MRSA and MSSA at the same body site.

 $^{^{\}mathcal{C}}$ Four MRSA, 3 MSSA.

TABLE 3.

Clinical Characteristics of the 6 Participants Colonized with pSK41-positive Staphylococcus aureus among Study Participants with Chronic Lower-Extremity Wounds in Southeastern Michigan, 2011

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Male	Male	Female	Male	Male	Male
Age, years	57	56	09	63	62	5
Race	White	Black	Black	Black	Black	White
Medical comorbidities	Hyperlipidemia, PAD	DM, HTN	DM, hyperlipidemia, HTN, seizures	Diabetes mellitus, ESRD receiving dialysis	NTH	COPD, hyperlipidemia, HTN
Indwelling device in previous 3 months	PICC	None	None	Tunneled dialysis catheter	None	PICC
Problems with chronic wounds, years	>2	>2	>2	>2	>2	>2
Antimicrobials in previous 3 months	Ampillicin-sulbactam, ciprofloxaxcin, cephalexin, vancomycin	None	TMP-SMX	None	TMP-SMX	Levofloxacin, TMP-SMX
Hospitalizations in previous 12 months	æ	0	-	2	0	0
Frequency of wound care visits	Monthly	Weekly	Weekly	Weekly	Unknown	Every 3 months
Nares culture	pSK41(+) MSSA	pSK41(+) MRSA	pSK41(-) MSSA	pSK41H(-) MRSA	pSK41(+) MR	pSK41(+) MSSA
Wound culture	pSK41(+) MRSA, no growth of VRE	pSK41(+) MRSA, no growth of VRE	pSK41(–) MRSA, no growth of VRE	pSK41H(-) MSSA, no growth of VRE	pSK41(-) MRSA, no growth of VRE	pSK41(-) MSSA, no growth of VRE
Perirectal culture	pSK41(+) MSSA, no growth of VRE	Not performed	pSK41(+) MRSA, no growth of VRE	No growth of S. aureus or VRE	No growth of S. aureus or VRE	Not performed

NOTE. COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; MRSA, methicillin-resistant Staphylococcus aureus, MSSA, methicillin-susceptible S. aureus, PAD, peripheral arterial disease; PICC, peripherally inserted central catheter; TMP-SMX, trimethoprim-sulfamethoxazole; VRE, vancomycin-resistant enterococcus.