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Major Article

Predictors of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci co-colonization among nursing facility patients

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Background: The emergence of vancomycin-resistant *Staphylococcus aureus* (VRSA) poses significant challenges for antibiotic therapy. We characterized the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) co-colonization that may facilitate resistance transfer and vancomycin-resistant *S aureus* emergence among nursing facility patients.

Methods: We cultured newly admitted patient hands, nares, oropharynx, groin, and perianal region plus wounds and device insertion sites, if applicable, upon enrollment at day 14, day 30, and monthly follow-up up to 6 months. Demographic, comorbidity, and antimicrobial use data were collected. Functional status was assessed at each visit using the Physical Self-Maintenance Scale. Multinomial logistic regression was performed to determine factors predictive of co-colonization.

Results: Five hundred eight patients were enrolled, with an average follow-up time of 28.5 days. Prevalence of MRSA/VRE co-colonization, MRSA alone, and VRE alone was 8.7%, 8.9%, and 23.4%, respectively. Independent predictors of co-colonization included indwelling device use (odds ratio [OR] = 5.5 [2.2-13.7]), recent antibiotic use (OR = 2.5 [1.4-4.2]), diabetes (OR = 1.9 [1.0-3.8]), and the presence of open wounds (OR = 1.9 [1.0-3.6]).

Conclusions: High rates of VRE are driving co-colonization with MRSA in nursing facilities. Indwelling device use, recent antibiotic use, diabetes, and open wounds predicted patient co-colonization.

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are a significant cause of morbidity and mortality in healthcare settings.[1,2] Because of their inherent resistance to beta-lactams and often additional resistance to other classes of antibiotics, including macrolides, fluoroquinolones, and aminoglycosides, therapeutic options are limited.[3] Traditionally, glycopeptides such as vancomycin have been the antibiotic treatment of choice for MRSA infections; however, in recent years, the emergence of glycopeptide resistance has increasingly resulted in treatment failure and worse clinical outcomes.[3–5] Importantly, vancomycin-resistant *Staphylococcus aureus* (VRSA) strains (minimum inhibitory concentration ≥ 16 μg/mL) have been discovered, with 14 cases reported in the United States since 2002.[6,7] While the emergence of VRSA has been slow, the continued development of glycopeptide resistance among MRSA is concerning and presents unique treatment challenges, as infections with these organisms require utilization of alternative, and often suboptimal, treatment regimens.[3]

Studies have demonstrated that VRSA occurs when MRSA acquires a *vanA* gene through genetic conjugation with vancomycin-resistant enterococci (VRE), which imparts vancomycin resistance via alteration of the peptidoglycan structure of the cell wall.[8–10] In the majority of VRSA cases, vancomycin-resistant *Enterococcus faecalis* has been the *vanA* donor versus other VRE species. To facilitate conjugation, both bacterial species must be in close proximity to each other by co-colonizing a single site of a patient's body.[9,10] While patterns of MRSA and VRE co-colonization have been studied in hospitalized patients,[9,11–13] other healthcare settings may present unique

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environments for the dissemination of resistance. Specifically, nursing facilities (NFs) are known reservoirs for multidrug-resistant organisms (MDROs), with an estimated one-third of all NF patients being colonized with one or more MDROs.[3,14] Patients are admitted to these facilities for rehabilitation following discharge from acute care hospitals, and they have high rates of bacterial colonization based on several factors, including impaired functional status, widespread antibiotic use, and frequent long-term use of indwelling devices such as urinary catheters and feeding tubes.[15–19] One study in 2011 analyzed colonization patterns of MRSA and VRE among NF patients who had indwelling devices and identified decreased functional status and the presence of wounds as significant risk factors for MRSA and VRE co-colonization.[20] Although an important first step, it is difficult to generalize these findings, as those with indwelling devices represent a specific high-risk population that makes up a fraction of all NF patients.[21–23]

Given the possibility of resistance transfer between MRSA and VRE, our primary objective was to investigate the epidemiology of MRSA and VRE co-colonization among a predominantly short-stay, postacute NF population regardless of indwelling device use. Specifically, we were interested in defining risk factors for MRSA and VRE co-colonization that may lead to better identification of high-risk patients and guide the implementation of targeted intervention practices. We hypothesized that decreased functional status would predict co-colonization in this population.

METHODS

Study population and design

This study analyzed microbial culture data collected as part of a larger prospective cohort study that aimed to identify patterns of MDRO colonization and dissemination between newly admitted NF patients, healthcare workers, and the environment.[24] The parent study enrolled newly admitted patients from 6 NFs in Southeast Michigan between November 2013 and November 2015 and was approved by the University of Michigan Institutional Review Board. For this analysis, we considered patients who were enrolled in the study within 7 days of arriving at the facility. Informed consent was obtained from all participants or the durable power of attorney. Patients were followed for a maximum of 180 days or until discharge from the facility, death, or requesting withdrawal. Patients were excluded from the study if they did not provide informed consent, did not speak English, or were receiving end-of-life care.

Clinical data collection

To determine bacterial colonization status, patient cultures were obtained at each visit using Culturette swabs (Becton Dickinson, Franklin Lakes, NJ) at multiple anatomic sites, including the nares, oropharynx, groin, perianal area, and hands. Cultures of open wounds and indwelling device insertion sites were also collected if accessible. Indwelling devices included suprapubic catheters and enteral feeding tubes. Samples were collected upon enrollment, 14 days following enrollment, and every 30 days thereafter for up to 180 days.

Demographic and relevant clinical information, including gender, age, indwelling device use, recent antibiotic usage, the presence of open wounds, and underlying comorbidities, was obtained through patient chart review for inclusion in risk factor analysis. Comorbidities were assessed at baseline using the Charlson Comorbidity Index, with higher scores indicating increased comorbidity.[25] Wounds with any discharge noted, vascular ulcers, diabetic ulcers, and pressure ulcers greater than stage 1 were all considered “open wounds.” Functional status was assessed for each patient at baseline and at each follow-up visit using the Physical Self-Maintenance Scale and given a score ranging from 6-30, reflecting increasing severity of functional decline.[26] For patients with $\geq$30 days of follow-up, data were also collected on repeat hospitalizations since admission to their facility.

Microbiologic methods

Swab samples were streaked onto tryptic soy agar containing 5% sheep blood, mannitol salt agar, and bile esculin agar containing 6 μg/mL vancomycin and incubated at 35°C for 24 hours. Patient hand swabs were first placed in brain heart infusion broth and incubated at 35°C overnight before being streaked onto plates. Bright yellow colonies grown on mannitol salt agar were isolated, and *S aureus* identification was confirmed by positive catalase and coagulase using Staphaurex (Remel, Lenexa, KS) tests. Methicillin resistance was tested using cefoxitin disk diffusion. Colonies causing a black coloration on bile esculin-vancomycin plates were isolated, and VRE identification was confirmed by a positive pyrrolidonyl arylamidase test. VRE isolate speciation was achieved by following the modified polymerase chain reaction assay protocol developed and validated by Tan et al.[27]

Colonization definitions

For analysis of anatomic site level incidence, co-colonization was defined as the isolation of both MRSA and VRE from a single anatomic site on the same visit. For all other analyses, patients were considered co-colonized with MRSA and VRE if they had positive cultures for both species at any combination of anatomic sites on the same visit. This definition was previously used by Flannery et al.[20] when investigating MRSA and VRE co-colonization among long-stay NF populations with indwelling devices, and by requiring same-day isolation of organisms, it is more conservative than those used in other studies investigating co-colonization in acute care settings.[9,11–13,20]

Statistical analysis

Significant differences between baseline characteristics of patients who were co-colonized at some point during the study and those who were never co-colonized were identified using χ^2 and 2-sample t tests where appropriate. The prevalence of MRSA and VRE co-colonization, MRSA colonization alone, and VRE colonization alone was calculated as the percentage of total visits during which patients were positive for colonization to reflect the dynamic nature of bacterial colonization over time. To calculate overall incidence rates of colonization, dates of bacterial acquisition were set at the midpoint between the date of the most recent negative swab culture and the date of the first positive swab culture. For example, if a patient was not colonized on day 30 but was co-colonized on day 60, then the date of bacterial acquisition was set at day 45. Calculation of anatomic site specific incidence rates was conducted using only patients with $\geq$1 follow-up visit and no missing anatomic site swabs to more accurately reflect true incidence rates. Because of limited access to patient wounds and indwelling device insertion points for culturing, incidence rates were not calculated at these sites. Cox regression analysis was performed with a primary endpoint of co-colonization to identify patient risk factors for decreased time to co-colonization with MRSA and VRE. Additionally, we used a generalized linear mixed effect model via multinomial logistic regression to determine the effect of clinical and demographic characteristics on colonization at any point. Colonization at any point was defined as no colonization, MRSA only, VRE only, and co-colonization. This model allowed for adjustments based on random error and potential longitudinal correlation effects within individual patients as their colonization statuses changed from one visit to the next. All statistical analyses were performed using Stata 13 (StataCorp LLC, College Station, TX).

RESULTS

Study group characteristics

In total, there were 1,384 eligible, newly admitted NF patients across all 6 facilities, of which 508 (36.7%) were enrolled in this study within 7 days of admission. The main reasons for nonenrollment were patient refusal (n = 458, 33.1%) or family or legal guardian refusal (n = 172, 12.4%). An average of 85 patients were enrolled per facility (range 43-128) and were followed for a total of 1,266 visits. The average length of stay was 28.5 days. The number of cultures obtained from each anatomic site varied due to differences in site accessibility among patients, resulting in a total of 1,103 hand cultures, 1,096 nares cultures, 1,062 oropharynx cultures, 1,102 groin cultures, and 727 perianal cultures. Of these patients, 13.2% were co-colonized with both MRSA and VRE at any point during the study. Co-colonized patients were more likely to have used antibiotics in the previous 30 days, to have increased severity of underlying comorbidities and decreased functional status, and to have open wounds upon enrollment compared with patients who were not colonized at all or colonized only with MRSA or VRE alone (Table 1).

MRSA and VRE prevalence and incidence

At baseline, 7.5% of patients were co-colonized with MRSA and VRE, 8.1% were colonized with MRSA alone, and 26.2% were colonized with VRE alone. In total, 414 MRSA isolates and 686 VRE isolates were obtained. Of the VRE isolates, 306 (44.6%) were *Enterococcus faecium* and 267 (38.9%) were *E faecalis*. Overall prevalence of MRSA and VRE co-colonization was 8.7%, 8.9% for MRSA alone and 23.4% for VRE alone. Incidence rates were calculated to further describe new colonization acquisition in patients who were not colonized upon enrollment (Fig 1). Overall, co-colonization occurred at a rate of 3.0 per 1,000 patient days (95% confidence interval [CI], 2.1-4.3), MRSA colonization alone at a rate of 4.0 per 1,000 patient days (95% CI, 2.9-5.5), and VRE colonization alone at a rate of 9.0 per 1,000 patient days (95% CI, 6.9-11.6). Univariate Cox regression analysis demonstrated that indwelling device use, antibiotic use within the previous 30 days, the presence of open wounds, and being previously colonized with either MRSA or VRE were all risk factors for becoming co-colonized during patient stays (Table 2). In the multivariate analysis, however, only indwelling device use and being previously colonized with MRSA or VRE were significant predictors of becoming co-colonized, with hazard ratios of 4.2, 17.0, and 6.3, respectively (95% CI, 1.4-12.7, 5.3-54.6, 2.2-18.2) (Table 2). Co-colonization was most frequent on patient hands (Fig 1).

Table 1
Baseline demographic and clinical characteristics for 508 nursing facility patients

Characteristic	Overall n = 508	Co-colonized n = 38	Not co-colonized n = 470	*P* value
Mean ± SD				
Follow-up days	28.5 (44.2)	40.9 (51.0)	27.5 (43.5)	**.03**
Age, y	73.8 (12.1)	74.5 (12.4)	73.8 (12.1)	.36
CCI	2.6 (2.1)	3.5 (2.0)	2.5 (2.1)	**.003**
PSMS	14.0 (4.4)	15.4 (4.7)	13.9 (4.3)	**.02**
No. (%) of patients				
Male	219 (43.1)	19 (50)	200 (42.6)	.37
Diabetes	204 (40.2)	19 (50)	185 (39.4)	.20
Recent antibiotic use*	305 (61.7)	29 (78.4)	276 (60.4)	**.03**
Device use at baseline	48 (9.5)	6 (15.8)	42 (8.9)	.17
Open wound at baseline†	84 (17.8)	10 (31.3)	74 (16.9)	**.04**

Note. Bold values are statistically significant ($P < .05$).
CCI, Charlson Comorbidity Index; *PSMS*, Physical Self-Maintenance Scale; *SD*, standard deviation.
*n = 494.
†n = 471.

Association of colonization status with demographic and clinical characteristics

Multivariate analysis using a generalized linear mixed model found indwelling device use, antibiotic use within the previous 30 days, diabetes, and the presence of open wounds to be significant independent predictors of patient co-colonization with MRSA and VRE (Table 3). Patients with indwelling devices in place were 5.5 times as likely to be co-colonized compared with those without devices (95% CI, 2.2-13.7) Those with recent antibiotic use were 2.5 times as likely to be co-colonized (95% CI, 1.4-4.2). Patients with diabetes were 1.9 times as likely to be co-colonized (95% CI, 1.0-3.8). Those with open wounds were 1.9 times as likely to be co-colonized (95% CI, 1.0-3.6).

DISCUSSION

In this prospective cohort study, we conducted active surveillance for the presence of MRSA and VRE co-colonization of 508 newly admitted patients at 6 different NFs in order to further characterize the epidemiology of these organisms in this unique setting, which is a well-recognized reservoir for MDROs. Patients enrolled in our study consisted primarily of a postacute short-stay population. Co-colonization with MRSA and VRE was frequent and perhaps driven by a high prevalence of VRE in our study population. At the anatomic site level, and unique to our study, we show that patient hands are the most common site of concurrent co-colonization with MRSA and VRE. This finding emphasizes the role of patient hand contamination in transmission of MDROs and may have implications for future targeted infection prevention measures. Lastly, indwelling device use, recent antibiotic use, diabetes, and open wounds were all found to be independent predictors of co-colonization at any point during the study.

Overall, patients enrolled in this study comprised a population undergoing relatively short stays, with an average follow-up time of 28.5 days. All patients were admitted to an NF following hospitalization, and nearly 42% of patients were colonized with MRSA and/or VRE upon admission. Co-colonization was common among our study population, with an overall prevalence of 8.7%. In NFs, while MRSA and VRE colonization alone has been investigated by multiple studies, limited data exist investigating the prevalence of co-colonization in these settings. One study investigating co-colonization in nursing homes found an overall prevalence of 7.9%, but this study differed from ours, in that it focused specifically on a high-risk subgroup of long-stay residents with indwelling devices that may not be comparable to our patient population.[20] MRSA/VRE co-colonization in hospitalized patients has been better studied with prevalence estimates that vary widely, ranging from 2.7%-28.6%.[9,11–13] This type of discrepancy across studies can be explained by differences in study populations, whether surveillance or clinical cultures were collected, and variability in co-colonization definitions. There is a need for consistency across future studies in order to appropriately track and compare MRSA and VRE co-colonization in different settings.

Furthermore, our study describes an evolving MDRO epidemiology in postacute care facilities, with a rising prevalence of VRE colonization of 23.4% compared with previously reported prevalence estimates ranging from 5%-18%.[3,14,28] Likewise, 38.9% of these cases were vancomycin-resistant *E faecalis*, which has been associated with transferring glycopeptide resistance in the majority of VRSA cases.[9,10] There is a known increased prevalence of VRE bacterial populations in Southeast Michigan compared with the rest of the country, which may explain this finding. We believe that the transmission of VRE among facility patients is a key driving force of co-colonization with

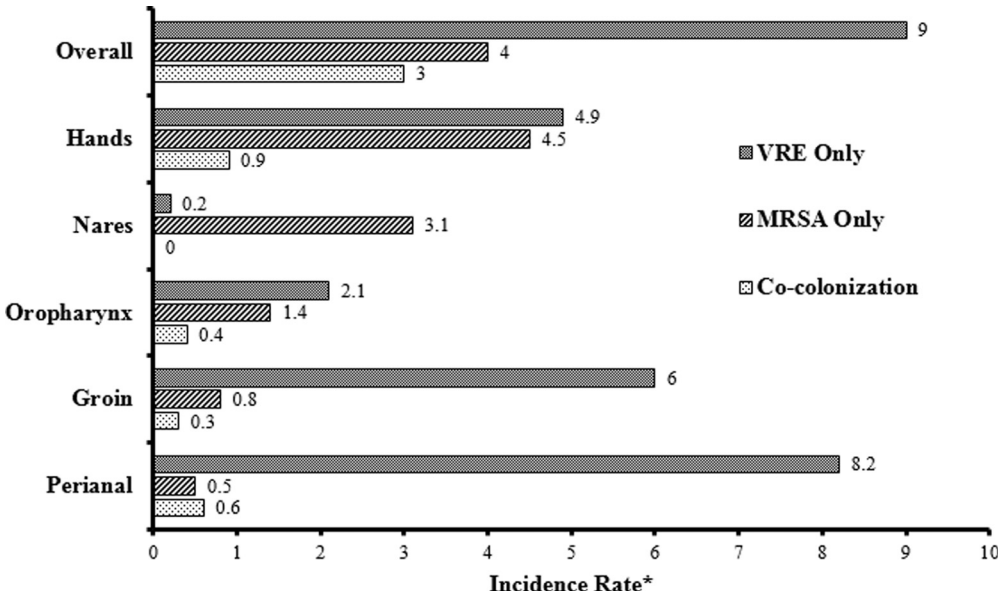

Fig 1. Incidence of MRSA and VRE colonization. Incident rates reported per 1,000 patient days. *MRSA*, methicillin-resistant *Staphylococcus aureus*; *VRE*, vancomycin-resistant enterococci.

MRSA.[29] This is evidenced by the high incidence of VRE colonization, occurring at over 2 times the rate of MRSA colonization. Our regression analysis demonstrated that being previously colonized with MRSA alone placed patients at nearly 3 times the risk of acquiring VRE and becoming co-colonized. Whether this co-colonization increases infection rates with either MRSA or VRE is beyond the scope of this study and needs further investigation to evaluate intervention effectiveness.

When determining what targeted intervention practices to implement, it is important to understand anatomic patterns of bacterial colonization on a patient's body. Anatomic site level analysis revealed that same-site MRSA and VRE co-colonization and MRSA colonization alone occurred most frequently on patient hands, while VRE colonization alone occurred most frequently in the perianal region. VRE, a common colonizer of the gastrointestinal tract, may easily translocate to other anatomic sites, leading to co-colonization. VRE was also commonly present on patient hands and groins. Methods of translocation are varied and may include self-inoculation by patients and the provision of more contact-intensive care, such as toileting, bathing, and dressing, by healthcare workers.[14,20,21] This can be addressed through a variety of interventions, including patient and healthcare worker hand hygiene and the enforcement of standard precautions, such as face masks, gloves, and gowns, whenever there is a risk of exposure to body fluid or mucosae. In addition, education of healthcare workers and provision of feedback are critical, because several studies have shown that the healthcare personnel in these settings are often suboptimally trained in the fundamentals of infection prevention and control, resulting in decreased adherence to infection prevention measures.[30,31]

Table 2
Risk factors for time to new acquisition of methicillin-resistant *Staphylococcus aureus*/vancomycin-resistant enterococci co-colonization

	Univariate analysis			Multivariate analysis		
Characteristic	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.0	.97-1.0	.97	1.0	.97-1.0	.75
PSMS	1.0	.93-1.1	.92	.96	.88-1.1	.41
CCI	.95	.79-1.1	.58	.93	.73-1.2	.55
Device use	3.3	1.4-7.8	**.006**	4.2	1.4-12.7	**.01**
Antibiotic use	2.1	1.0-4.4	**.05**	1.0	.42-2.6	.94
Diabetes	.82	.38-1.8	.61	1.1	.42-2.8	.86
Open wounds	3.0	1.4-6.6	**.005**	2.2	.95-5.1	.07
Hospitalization	1.8	.62-5.2	.28	1.3	.43-4.1	.62
Previous MRSA*	6.3	2.8-14.1	**<.001**	17.0	5.3-54.6	**<.001**
Previous VRE†	3.0	1.4-6.2	**.004**	6.3	2.2-18.2	**.001**

Note. Bold values are statistically significant ($P < .05$).
CCI, Charlson Comorbidity Index; *CI*, confidence interval; *HR*, hazard ratio; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *PSMS*, Physical Self-Maintenance Scale; *VRE*, vancomycin-resistant enterococci.
*Colonized with MRSA alone at previous visit.
†Colonized with VRE alone at previous visit.

In addition to targeted intervention practices, identifying patients at high risk for bacterial colonization also guides the implementation of screening measures that may lead to reduced rates of MRSA and VRE co-colonization in postacute care settings. In this study, we identified the use of indwelling devices, antibiotic use within the previous 30 days, diabetes, and open wounds as significant independent predictors of being co-colonized at any point during a patient's stay. The use of indwelling devices is a well-known risk factor for MDRO colonization, as these devices compromise host defenses and mandate more contact-intensive care, placing patients at increased risk for the acquisition of new bacteria as well as transmitting bacteria to healthcare workers and the environment.[14,22,32,33] Antibiotic use and open wounds have been shown in other studies to be predictors of co-colonization, and diabetes has been demonstrated to increase the risk of MRSA and VRE colonization in other healthcare settings.[3,11–12,24,34–37] Further studies are needed to investigate the benefits of identifying these high-risk individuals and implementing specific infection prevention measures, such as collecting surveillance cultures, utilizing proper contact and isolation precautions, and hand hygiene, on patient co-colonization rates.

Our study has several limitations. First, the majority of our patients were short-stay, and the epidemiology of co-colonization may be different in long-stay populations; therefore, these findings are not generalizable to all NFs. Second, during some visits participants refused perianal and wound cultures, which could underestimate co-colonization rates. Additional studies are needed to investigate the ability of wounds to facilitate MRSA and VRE

Table 3
Effect of covariates on colonization from multinomial logistic regression (n = 508 patients)

	Co-colonization versus no colonization			MRSA only versus no colonization			VRE only versus no colonization		
Characteristic	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.0	.98-1.0	.88	1.0	.97-1.0	.84	1.0	.96-1.0	.82
Follow-up days	1.0	.99-1.0	.61	1.0	.99-1.0	.54	.99	.99-1.0	**.01**
PSMS	1.0	.91-1.1	.27	1.1	.99-1.1	.10	1.0	.96-1.1	.64
CCI	1.1	.94-1.3	.21	1.1	.90-1.2	.50	1.2	1.1-1.4	**.007**
Device	5.5	2.2-13.7	**< .001**	1.6	.56-4.4	.39	2.1	.90-5.0	.09
Antibiotic use	2.5	1.4-4.2	**.001**	.73	.41-1.3	.28	3.3	2.2-5.1	**≤ .001**
Diabetes	1.9	1.0-3.8	**.05**	1.1	.58-2.3	.70	1.9	1.0-3.3	**.04**
Open wounds	1.9	1.0-3.6	**.04**	2.0	1.1-3.8	**.03**	1.5	.89-2.6	.13
Hospitalized	.81	.46-1.4	.45	1.1	.62-1.9	.78	.83	.55-1.3	.39

Note. Bold values are statistically significant ($P < .05$).
CCI, Charlson Comorbidity Index; *CI*, confidence interval; *OR*, odds ratio; *PSMS*, Physical Self-Maintenance Scale.

co-colonization as well as the effect adequate wound care, including scheduled dressing changes, wound cleaning, and the use of barrier precautions, has on the incidence of co-colonization.

We also note several strengths. This is one of the largest microbial studies with active surveillance of multiple anatomic sites for MRSA and VRE in postacute care settings and extends findings from other studies based on less extensive culturing practices. In addition, since this study collected cultures from all newly admitted patients, we were able to define epidemiology of MRSA and VRE co-colonization at a population level.

CONCLUSIONS

MRSA and VRE are prevalent in long-stay settings, and future studies are needed to further investigate the role VRE transmission, the presence of wounds, and targeted screening and prevention measures play in patient co-colonization.

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