Identifying Groups at High Risk for Carriage of Antibiotic-Resistant Bacteria

Jon P. Furuno, PhD; Jessina C. McGregor, PhD; Anthony D. Harris, MD, MPH; Judith A. Johnson, PhD;
Jennifer K. Johnson, PhD; Patricia Langenberg, PhD; Richard A. Venezia, PhD; Joseph Finkelstein, MD;
David L. Smith, PhD; Sandra M. Strauss, BS, M(ASCP); Eli N. Perencevich, MD, MS

Background: No simple, cost-effective methods exist to identify patients at high risk for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci colonization outside intensive care settings. Without such methods, colonized patients are entering hospitals undetected and transmitting these bacteria to other patients. We aimed to develop a highly sensitive, simple-to-administer prediction rule to identify subpopulations of patients at high risk for colonization on hospital admission.

Methods: We conducted a prospective cohort study of adult patients admitted to the general medical and surgical wards of a tertiary-care facility. Data were collected using electronic medical records and an investigator-administered questionnaire. Cultures of anterior nares and the perirectal area were also collected within 48 hours of admission.

Results: Among 699 patients who enrolled in this study, 697 underwent nasal cultures; 555, perirectal cultures; and 553, both. Patient self-report of a hospital admis-sion in the previous year was the most sensitive variable in identifying patients colonized with methicillin-resistant *Staphylococcus aureus* or with either organism (sensitivity, 76% and 90%, respectively). A prediction rule requiring patients to self-report having received antibiotics and a hospital admission in the previous year would have identified 100% of patients colonized with vanco-mycin-resistant enterococci. In the high-risk groups defined by the prediction rule, the prevalence of coloniza-tion by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, or either organism were 8.1%, 10.2%, and 15.0%, respectively.

Conclusion: Patients with a self-reported previous ad-mission within 1 year may represent a high-risk group for colonization by methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci at hospital admission and should be considered for targeted active surveillance culturing.

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Author Affiliations:
Departments of Epidemiology and Preventive Medicine (Drs Furuno, McGregor, Harris, Langenberg, Finkelstein, Smith, and Perencevich and Ms Strauss) and Pathology (Drs J. A. Johnson, J. K. Johnson, and Venezia), University of Maryland School of Medicine, and Veterans Affairs Maryland Health Care System (Drs Harris, J. A. Johnson, and Perencevich), Baltimore; and Fogarty International Center, National Institutes of Health, Bethesda, Md (Dr Smith).

METHICILLIN-RESISTANT *Staphylococcus aureus* (MRSA) and vancomy-cin-resistant entero-cocci (VRE) are asso-ciated with considerable morbidity and mortality among infected patients.[1] Despite laborious and costly infection control efforts, the prevalence of these patho-gens continues to increase. In an effort to reduce nosocomial transmission of these organisms, the Society for Healthcare Epi-demiology of America has recommended culturing for patients at high risk for colo-nization by MRSA or VRE.[2]

Earlier risk factor studies have sug-gested that previous health care and anti-biotic exposures are associated with MRSA or VRE carriage on admission, yet the util-ity of these variables within a clinical pre-diction rule to identify patients at high risk for infection control interventions has not been quantified.[3-7] The objective of this study was to design a clinical prediction rule to identify a subpopulation of patients at high risk for colonization by MRSA or VRE, which could then be used to target active surveillance on hospital admission to non–intensive care unit wards. In addition, we aimed to use information easily obtained from patients by admitting physicians or nurses. This approach was chosen be-cause it would capture exposures that mani-fest outside the index hospital and result in the creation of a rule that could be imple-mented in community hospitals and ter-tiary-care centers without the need for au-tomated computerized data support.

METHODS

STUDY DESIGN AND PATIENT POPULATION

We conducted a prospective cohort study of patients admitted to the University of Mary-land Medical Center (UMMC), a 648-bed, ter-tiary-care center located in Baltimore. Before study commencement, the institutional re-view board reviewed and approved this study.

Sample size was based on the expected prevalence and sensitivity and specificity of the prediction rules. These factors were estimated by extrapolating data from a previously published report.[6] Our study was powered to have the highest possible precision (true-positive and true-negative rates) around the sensitivity and specificity estimates.

Patients were enrolled between December 16, 2003, and September 9, 2004. Each weekday, study personnel received a list of all adult patients eligible for the study who had been admitted during the previous 24 hours. Patients known to have been previously colonized or infected with MRSA or VRE were excluded. Patients admitted directly to an intensive care unit or to the Correctional Health Unit were also excluded because such units are high-risk subpopulations, and surveillance cultures are already collected from these patients at UMMC and often at other institutions.[8,9] We also excluded patients admitted directly to the psychiatric, trauma, and obstetrics wards because these wards represent subpopulations of patients different from those under study.

A random sample of patients from the daily list was generated using a pocket computer (Microsoft Corp, Redmond, Wash) and embedded Visual Basic algorithm (Version 3.0; Microsoft Corp). Patients were approached in their rooms and invited to participate. Patients providing informed consent were administered a questionnaire, and a study nurse collected anterior nares and perirectal specimens for cultures within 24 hours of enrollment. The purpose of the questionnaire was to collect data not available in patients' medical records (eg, previous hospital admissions or antibiotic exposures outside the index hospital). Data on medical history and current medical condition were also collected from all enrolled patients using the UMMC's central data repository of administrative, pharmacy, and laboratory data. These electronic data have been used extensively in epidemiologic studies of antibiotic resistance, and their validation assessments of positive and negative predictive values were in excess of 99% when compared with patients' hard-copy medical charts.[6,10-13] Two variables, previous admission within 1 year and previous antibiotic exposure within 1 year, were collected from the questionnaire and central data repository for comparison purposes.

LABORATORY METHODS

Anterior nares and perirectal culture swabs (Bactiswab; Remel Co, Lenexa, Kan) were plated on blood agar (trypticase soy agar with 5% sheep blood) and phenylethyl alcohol agar plates (Remel Co). Perirectal culture swabs were also placed in a bile esculin azide enrichment broth (Enterococcosel broth; BBL Microbiology Systems, Becton, Dickinson and Company, Sparks, Md) to improve recovery of enterococci. Bile esculin azide broths positive for esculin hydrolysis were plated on vancomycin-screening agar (10-µg/mL vancomycin). Enterococci were identified using the biochemical scheme of Facklam and Collins[14] in conjunction with an automated susceptibility testing system with gram-positive susceptibility cards (Vitek GPI cards; bioMérieux Vitek Inc, Hazelwood, Mo). The VRE were defined as *Enterococcus faecium* or *Enterococcus faecalis* isolates with vancomycin minimum inhibitory concentrations of 32 µg/mL or more as determined by minimum inhibitory concentrations (Etest; AB Biodisk, Solna, Sweden). *Staphylococcus aureus* was identified by latex agglutination (Staphaurex; Remel Co) and/or coagulase positive reactions (Bactistaph; Remel Co). Confirmed *S aureus* cultures were screened on Mueller-Hinton agar with 4% sodium chloride and 6-µg/mL oxacillin to test for the presence of MRSA. Additional susceptibility testing was performed by means of disk diffusion according to Clinical and Laboratory Standards Institute (formerly known as the National Committee for Clinical Laboratory Standards) guidelines.[15,16] All anterior nares MRSA isolates underwent typing to assess the proportion that contained the community-associated staphylococcal chromosome cassette *mec* (SCC*mec*) type IV, by the methods previously used by Hiramatsu et al.[17]

STATISTICAL ANALYSES

Means and frequency distributions were used to describe the characteristics of the study population. We calculated sensitivity, specificity, and 95% confidence intervals to assess the ability of variables to identify patients colonized and not colonized with MRSA or VRE on hospital admission. We then created a prediction rule by including the variable with the highest sensitivity, followed by the addition of other variables using the Boolean logic terms (*and/or*) to assess whether they improved the sensitivity without resulting in a decrease in specificity. For example, if we were interested in the sensitivity of variables A and B, use of the Boolean term *and* would require patients to have A and B, and use of the Boolean term *or* would require the patient to have A or B. In general, use of the Boolean term *and* for combining variables will result in increased specificity, but will decrease sensitivity, and use of the Boolean term *or* will increase sensitivity but decrease specificity. The final rules to predict patients at high risk for colonization by MRSA, VRE, or either organism contained the variable or variables meeting these criteria. All analyses were performed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC).

COST ANALYSIS

We performed cost analyses to estimate projected cost savings from use of an active surveillance program guided by a prediction rule compared with a program that attempts to obtain surveillance cultures on all patients admitted to non–intensive care unit wards of the hospital. Costs were determined using published estimates of surveillance costs for MRSA alone, VRE alone, and both VRE and MRSA.[18,19] Per-person costs included nursing time for obtaining cultures and microbiological laboratory supplies and technician time for processing specimens. These costs were then multiplied by the number of patients who would have undergone active surveillance culturing under each of the competing scenarios, assuming 100% compliance with obtaining necessary cultures. We then compared surveillance culture costs to determine estimated program costs under each scenario. All costs were converted to 2004 US dollars by means of the medical services component of the Consumer Price Index.[20]

RESULTS

During the 8-month study period, 4710 eligible patients were admitted to UMMC. Of these, 2819 patients (59.9%) were randomly selected and underwent screening for possible participation, and 770 patients (16.3%) were enrolled. The primary reasons for not participating were that patients refused (n=463); patients were already undergoing contact isolation precautions for previous or current colonization or infection by antibiotic-resistant bacteria or an airborne pathogen (n=424); patients were out of their hospital rooms for tests or procedures (n=503); patients were asleep or not easily aroused (n=219); or patients had already been discharged when approached for consent (n=167). Differences between patients who enrolled and (1) all eligible

Table 1. Comparison Between Patients in the Final Study Sample and Patients Who Did Not Enroll or Underwent Screening but Did Not Enroll

Variable	Final Sample (n = 699)	Not Enrolled (n = 4011)	P Value*	Underwent Screening but Not Enrolled (n = 2120)	P Value†
Age, mean (SD), y	51.9 (15.7)	54.2 (16.1)	<.01	54.1 (16.2)	<.01
Male, No. (%)	342 (48.9)	2062 (51.4)	.22	1120 (52.8)	.08
Length of stay, median (IQR), d	3.0 (1.8-5.3)	3.1 (1.8-6.1)	.58	3.2 (1.8-6.2)	.26
In-hospital mortality, No. (%)	3 (0.4)	87 (2.2)	<.01	45 (2.1)	<.01
Admission to an ICU, No. (%)	34 (4.9)	285 (7.1)	.03	151 (7.1)	.04
Previous admission to index hospital within 1 y, No. (%)	365 (52.2)	1805 (45.0)	<.01	1086 (51.2)	.65

Abbreviations: ICU, intensive care unit; IQR, interquartile range.
*Represents comparison between patients who were enrolled and not enrolled in the final study.
†Represents comparison between patients enrolled in the final study and patients who underwent screening but did not enroll.

Table 2. Characteristics of the Sample Population of 699 Patients*

Variable	Frequency, No. (%)
Demographic variables	
Male	358 (51.2)
HCW or lives with an HCW†	89 (12.7)
Lives with someone admitted to hospital within 1 y†	91 (13.0)
Visited by an HCW at home†	113 (16.2)
Lives with a child or children younger than 4 y†	83 (11.9)
Child younger than 4 y attends daycare ≥3 d/wk†	35 (5.0)
Variables from current admission‡	
Transfer from another hospital, nursing home, or rehabilitation facility†	117 (16.7)
Received antibiotics within 48 h of admission	340 (48.6)
Received antibiotics during any part of admission	429 (61.4)
Admission to an ICU	33 (4.7)
In-hospital mortality	3 (0.4)
Comorbidities	
HIV/AIDS	31 (4.4)
Malignancy	118 (16.9)
Cardiovascular disease	134 (19.2)
Diabetes mellitus	149 (21.3)
Liver disease	23 (3.3)
Renal disease	16 (2.3)
Variables from previous admission	
Hospital admission within 1 y†	457 (65.4)
Documented hospital admission within 1 y	352 (50.4)
ICU admission within 1 y	89 (12.7)
Receipt of antibiotics within 1 y†	480 (68.7)
Documented receipt of antibiotics within 1 y	276 (39.5)

Abbreviations: HCW, health care worker; HIV, human immunodeficiency virus; ICU, intensive care unit.
*Mean age of the study sample was 52 years (SD, 16 years).
†Variable was self-reported.
‡Median length of stay was 3.0 days (interquartile range, 2.0-5.0 days).

patients or (2) patients who underwent screening but did not enroll are displayed in **Table 1**. Of the 770 patients enrolled, 709 (92.0%) underwent anterior nares and/or perirectal cultures. Ten of those patients were excluded because of missing data, resulting in a total sample size of 699 patients.

Of the 699 patients, 553 (79.1%) underwent both nasal and perirectal cultures, and all but 2 underwent an-

terior nares cultures. Of these, 175 (25.1%) were nasally colonized with *S aureus*, and of these, 49 cultures (28%) yielded MRSA. Thus, the prevalence of MRSA in the anterior nares was 7.0%. We attempted SCC*mec* typing on all 49 isolates, and 29 were identified as SCC*mec* type I; 10, SCC*mec* type II; and 8, SCC*mec* type IV. Two isolates could not be typed. We also isolated MRSA from 6 (1.1%) of 555 perirectal cultures, and among patients who received both cultures, 2 were colonized with MRSA at both sites. However, only patients nasally colonized with MRSA were included in this analysis, because infection control surveillance for MRSA typically is limited to collection of anterior nares cultures. The prevalence of VRE colonization among perirectal cultures was 5.2% (29/555), and the prevalence of colonization by MRSA or VRE among patients who received both cultures was 11.0%. One patient was cocolonized with MRSA and VRE.

Characteristics of the 699 patients in the sample population are displayed in **Table 2**. The mean (SD) age of the study sample was 52 (16) years, and 51.2% of patients were male. Notably, 352 patients (50.4%) were identified using the UMMC central data repository as having been admitted to the index hospital within 1 year, but questionnaire data suggest that the proportion of patients previously admitted to any hospital in the previous year was 65.4% (457/699). Thus, 105 patients (15.0%) may have had admissions within the past year that occurred at hospitals other than the index hospital and would not have been detected by a hospital automated computer system. Similarly, 39.5% of patients were identified using the central data repository as having received antibiotics during an admission to the index hospital in the previous year, but the questionnaire data suggest the prevalence of antibiotic exposure as an inpatient or an outpatient was 68.7%.

Although the sensitivity and specificity of all questionnaire variables and many candidate variables from the patients' medical records were calculated, only self-reported previous admission within 1 year and self-reported previous antibiotic exposures within 1 year demonstrated sensitivity in excess of 60% (**Table 3**). Both self-reported variables had considerably higher sensitivity but lower specificity than the same variables as de-

Table 3. Sensitivity and Specificity of Variables for Predicting Colonization With MRSA or VRE*

Variable	MRSA		VRE		MRSA or VRE	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Hospital admission within 1 y†	76 (61-87)	35 (32-39)	100 (88-100)	36 (32-40)	90 (80-96)	37 (32-41)
Documented hospital admission within 1 y	55 (40-69)	50 (46-54)	76 (57-90)	50 (46-54)	69 (56-80)	51 (46-55)
Received antibiotics within 1 y†	69 (55-82)	32 (28-35)	100 (88-100)	34 (29-38)	84 (72-92)	34 (30-38)
Received antibiotics within 1 y	49 (34-64)	61 (57-65)	76 (57-90)	63 (59-67)	62 (49-74)	64 (59-68)
Combination variables						
Hospital admission and received antibiotics within 1 y†	61 (46-75)	50 (46-54)	100 (88-100)	52 (47-56)	82 (70-91)	53 (48-57)
Hospital admission or received antibiotics within 1 y†	84 (70-93)	17 (14-20)	100 (88-100)	18 (14-21)	92 (92-97)	18 (14-21)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
*Data are given as percentage (95% confidence interval).
†Variable was self-reported.

Table 4. Prevalence of MRSA or VRE Colonization Between All Patients and High- and Low-Risk Groups

Organism	No. of Patients	Prevalence, %* (% of Total Sample Size)			P Value
		All Patients	High-Risk Patients	Low-Risk Patients	
MRSA†	697	7.0 (100)	8.1 (65)	5.0 (35)	.12
VRE‡	555	5.0 (100)	10.2 (52)	0 (48)	<.01
MRSA or VRE†	553	11.0 (100)	15.0 (66)	3.2 (34)	<.01

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
*Prevalence in each group (high- or low-risk) also represents the positive predictive value of the prediction rule.
†High risk was defined as having a self-reported previous hospital admission within 1 year.
‡High risk was defined as having a self-reported previous hospital admission *and* self-reported receipt antibiotics within 1 year.

fined using the central data repository. Because we aimed to maximize sensitivity, further analyses were restricted to these self-reported variables. When combinations of these variables were created to assess whether the sensitivity and specificity could be improved, the results were different for MRSA and VRE.

The final prediction rules to identify patients at high risk for colonization by MRSA or either organism included only 1 variable, ie, having a previous hospital admission within 1 year. However, the prediction rule to identify patients at high risk for colonization by VRE requires patients to have been admitted to the hospital and to have received antibiotics within the previous year. Use of these rules identified 76% (95% confidence interval, 61%-87%) of patients colonized by MRSA, 100% (95% confidence interval, 88%-100%) of patients colonized by VRE, and 90% (95% confidence interval, 80%-96%) of patients colonized by either organism and would have required surveillance culturing of 456 (65.4%) of 697 patients for MRSA, 271 (48.8%) of 555 patients for VRE, and 368 (66.5%) of 553 patients for either organism. The MRSA prediction rule identified 6 (75%) of 8 MRSA anterior nares isolates with the community-associated SCC*mec* type IV.

Using our prediction rules to designate patients at high risk for colonization by MRSA, VRE, or either organism, we compared the prevalence of colonization among these patients (ie, the positive predictive value of the rules) with the prevalence in all other patients (**Table 4**). The difference in prevalence of MRSA colonization (8.1% in

high-risk patients compared with 5.0% in all other patients) was not statistically significant. However, significant differences were observed between groups for VRE or for colonization by MRSA or VRE. Prevalence of VRE in the high-risk group defined by the prediction rule was 10.2% compared with 0% in other patients, and prevalence of either organism was 15.0% in the high-risk group compared with 3.2% in other patients.

Cost analyses compared the projected costs associated with hospital-wide MRSA or VRE active surveillance compared with the projected costs if surveillance was directed by the created prediction rules during the 8-month study period. As displayed in **Table 5**, hospital-wide surveillance guided by the prediction rule would have saved a projected $19 295 if screening for MRSA and a projected $26 436 if screening for VRE compared with nondirected, hospital-wide surveillance for each organism.

COMMENT

These data suggest that a high proportion of patients who were previously unrecognized carriers are colonized with MRSA or VRE on hospital admission. In our study, 11.0% of patients were colonized with MRSA or VRE. Thus, limiting surveillance strategies to intensive care units would not identify a large proportion of colonized patients, who would serve as foci of spread within hospitals. Patients admitted to any hospital within 1 year likely represent a

Table 5. Estimated Surveillance Costs Associated With Prediction Rule for Targeted Active Surveillance Compared With Hospital-Wide, Nondirected Surveillance for MRSA and VRE During 8-Month Study Period

| | Estimated Costs, $ | | |
Organism	Hospital Wide (n = 4710)	High-Risk Patients*	Cost Savings
MRSA	55 698	36 403	19 295
VRE	58 412	31 976	26 436

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
*High risk was defined as having a self-reported previous hospital admission within 1 year for MRSA (n = 3062) or self-reported previous hospital admission and antibiotic exposure within 1 year for VRE (n = 2449).

high-risk group for colonization by MRSA or VRE and thus should be targeted for infection control interventions on hospital admission. Adding to this prediction rule a requirement of self-reported previous antibiotic exposure in the past year improved the efficiency of identifying VRE-colonized patients by increasing the specificity of this rule without reducing the sensitivity. These findings suggest that prediction rules using few criteria can identify a large proportion of patients colonized with MRSA or VRE on hospital admission, and that implementation of targeted active surveillance using these rules would result in considerable projected cost savings compared with hospital-wide, nontargeted surveillance.

The prediction rules were more sensitive at detecting VRE- compared with MRSA-colonized patients (100% vs 76%, respectively). One possible explanation for the reduced sensitivity of the MRSA rule is the increasing spread of MRSA in people without exposures to health care facilities.[21] We investigated this possibility by testing all MRSA isolates from the anterior nares for the presence of a specific genetic element, SCC*mec* type IV, which has been linked with community-associated MRSA. However, we observed that the MRSA prediction rule would have identified 75% of the SCC*mec* type IV isolates, which was similar to the sensitivity of the prediction rule in identifying MRSA among the entire cohort. Thus, we do not believe that the presence of community-associated MRSA adversely affected the sensitivity of the rule.

Previous studies have suggested that active surveillance screening for MRSA or VRE and subsequent infection control interventions may be cost-effective in reducing the transmission, even with very low endemic prevalence of these organisms.[2,18,22] Herein we report that prevalence of colonization in high-risk patients was 8.1% for MRSA, 10.2% for VRE, and 15.0% for either organism. In addition, cost analyses suggest that projected costs of active surveillance guided by the prediction rule would be considerably less than those of hospital-wide surveillance. However, a potential limitation of these analyses is that the cost savings were calculated using only study participants and then projected to the entire hospital population.

Use of questionnaires identified 15% more patients who had been admitted to a hospital within 1 year and 29% more patients who had received antibiotics in the past year than those identified using the hospital's electronic database, which was limited to data from admissions to the index hospital. This finding suggests that sole dependence on computerized medical records may not sufficiently describe a patient's medical history and risk status, especially at a large tertiary-care facility.

In creating these rules, we sought to maximize sensitivity at the expense of specificity because the costs associated with false-positive findings are likely lower than those associated with false-negative findings. Patients identified by these rules were considered at high risk for colonization, and we suggest that these patients should be targeted for active surveillance culturing. Costs associated with not identifying colonized patients (ie, false-negative findings) could be considerable depending on the capacity of the colonized patient to transmit resistant organisms to other patients. Patients identified as high risk and who are found not to be colonized with either organism (false-positive findings) would at most have had surveillance cultures collected from them, which causes minimal increased morbidity and is not costly to the patient or the hospital.

Thus far, discussion has been limited to the validity of these rules as measured by sensitivity and specificity. However, the effectiveness of these rules at other institutions will also depend strongly on their predictive values. Prevalence of colonization by MRSA, VRE, or either organism was higher than expected, especially considering that patients with previous positive cultures for either or both organisms were excluded from participating in this study. If the prevalence of these organisms is lower in other hospitals, the predictive value of these rules will also be lower. Thus, when considering whether to implement these rules, the prevalence of colonization on admission must be estimated as an a priori indicator of the likely clinical utility.

A potential limitation of this study was that patients who participated were significantly younger and apparently less ill than patients who did not participate. Although this observation may suggest that our data are not generalizable to all patients eligible for participation in this study, we believe that this does not invalidate our results. Vancomycin-resistant enterococci and often MRSA are opportunistic pathogens, and thus, the enrollment of a less severely ill study population likely biased our results toward a null effect by including patients less likely to be colonized and to have previous health care exposures.

A simple prediction rule may cost-effectively identify high-risk subpopulations of patients to target for active surveillance. Patients with a previous hospital admission within 1 year likely represent 1 of these high-risk groups. If VRE is the problematic endemic pathogen, then information on previous antibiotic use could also improve targeted active surveillance. Relying on computerized patient medical records for identifying high-risk patients would likely be inferior to a simple intake questionnaire administered as part of the hospital admission process. Validation studies of these rules in different settings, especially in the community, Veterans Affairs institutions, institutions that provide long-term care, and other hospitals, are necessary to examine their utility outside of tertiary-care facilities.

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