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Major article

Collateral benefit of screening patients for methicillin-resistant *Staphylococcus aureus* at hospital admission: Isolation of patients with multidrug-resistant gram-negative bacteria

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Background: Surveillance at hospital admission for multidrug-resistant (MDR) gram-negative bacteria (GNB) is not often performed, potentially leaving patients carrying these organisms unrecognized and not placed in transmission precautions until they develop infection. Veterans Affairs (VA) facilities screen all admissions for methicillin-resistant *Staphylococcus aureus* (MRSA) and place positive patients in contact precautions. We assessed how often patients with MDR GNB in clinical cultures obtained within 30 days following admission would have been in contact precautions because of a positive MRSA admission screen.
Methods: MRSA screening and MDR GNB culture results were extracted from a database of patients admitted to all VA acute care medical facilities from January 2009-December 2012.
Results: Of patients with MDR GNB-positive cultures within 30 days following admission, up to 44.3% (dependent on bacterial species) would have been in contact precautions because of a clinical positive admission MRSA nasal screen. Admissions with a positive MRSA screen had odds for MDR GNB in a culture 2.5 times greater than those with a negative screen (95% confidence interval [CI], 2.4-2.6). Odds ratios were 2.4 (95% CI, 2.3-2.5) for MDR *Enterobacteriaceae*, 2.7 (95% CI, 2.5-2.9) for MDR *Pseudomonas aeruginosa*, and 4.3 (95% CI, 3.8-4.8) for MDR *Acinetobacter* spp.
Conclusions: Patients may be serendipitously placed in contact precautions for MDR GNB when isolated for a positive admission MRSA screen.

Programs using active screening of the anterior nares for methicillin-resistant *Staphylococcus aureus* (MRSA) colonization have been associated with decreased MRSA transmissions and health care–associated infections (HAIs).[1-5] One of these programs also reported decreased HAIs because of vancomycin-resistant *Enterococci* and *Clostridium difficile*.[1] There may be an effect on nontargeted pathogens if MRSA-positive nasal surveillance tests serve as a marker for colonization with other multidrug-resistant organisms (MDROs). If this is true, then isolation for MRSA may result in the serendipitous isolation of patients harboring other MDROs, including multidrug-resistant (MDR) gram-negative bacteria (GNB).

Currently available rapid molecular tests and noninvasive sampling methods make screening for MRSA colonization relatively simple compared with screening for other MDROs. By Veterans Health Administration Directive,[6] after verbal informed consent, all

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facility admissions nationwide are screened for MRSA. Positive patients are placed in contact precautions[7] as soon as the results are returned. Because polymerase chain reaction (PCR) testing is usually used for admission screening, the median turnaround time from admission to reporting of the screening result is 12.5 hours.[8] Positive patients usually remain in contact precautions for the duration of their admission and are again placed in contact precautions without rescreening if readmitted within 1 year.

We evaluated a large national Veterans Affairs (VA) database to determine how frequently inpatients with MDR GNB-positive clinical cultures within 30 days following admission might have already been isolated if they had been placed in contact precautions for a positive MRSA screen at admission.

METHODS

Nasal screening and clinical culture results from patients admitted to VA acute care medical facilities from January 2009-December 2012 were extracted from national clinical microbiology laboratory data using an approach described previously.[9] Nasal screening was performed as previously described,[1] and a clinical culture was defined as a specimen obtained from any body site, fluid, or drainage other than the specimens obtained for screening. As a measure of nasal MRSA carriage status, all nasal screens for MRSA obtained 12 months prior to and within 24 hours after admission to an acute care facility were identified. MDR GNB were defined as organisms with acquired nonsusceptibility to a least 1 agent in $\geq$3 antimicrobial classes.[10] A history of MDROs was defined as MRSA, vancomycin-resistant *Enterococcus*, or MDR GNB isolated from a clinical culture or surveillance screen within 12 months prior to hospital admission. A new MDR GNB event was defined as recovery of an MDR GNB within 30 days following admission in a clinical culture, therefore capturing some MDR GNB that were present but unknown on admission or were hospital acquired. The MDR GNB of interest for this analysis included MDR *Enterobacteriaceae* (including extended-spectrum β-lactamase producing bacteria and carbapenem-resistant bacteria), MDR *Pseudomonas aeruginosa* (including carbapenem-resistant organisms), and MDR *Acinetobacter* spp (including carbapenem-resistant organisms). Bacteria from clinical cultures were isolated, identified, and characterized using standard procedures observed at each facility. Clinical cultures were restricted to those that underwent antimicrobial susceptibility testing.

Comparisons of proportions were made using the χ^2 test. Generalized linear mixed models were used to predict the binary outcome of MDR GNB-positive clinical cultures during or after admission from MRSA PCR screening results. Random effects of facilities were also incorporated. Stata version 12.1 (StataCorp, College Station, TX) was used.

This analysis was approved by the Research Review Committee of the VA Salt Lake City Health Care System and the Institutional Review Board of the University of Utah.

RESULTS

During the 4-year analysis period, there were 1.6 million VA acute care facility admissions (759,759 unique patients) nationwide that received a PCR MRSA nasal screen. Of these, 14.7% were positive at admission or had been positive within the prior year, and 6.3% had a history of a positive MDRO culture in the prior year. The percentage of admissions with MRSA-positive nasal screening or previous positive MDRO culture was 17.7%.

The frequencies of clinical cultures yielding MDR GNB within 30 days following admission were evaluated with respect to initial MRSA screening results. Overall, 2.4% of patients with a MRSA-positive screening had a subsequent new MDR GNB clinical culture compared with 0.9% of those with a negative MRSA screen ($P < .001$). Among admissions with a positive MRSA screen, the percentage that had a subsequent positive MDR GNB clinical culture varied by organism and ranged from 0.2% for MDR *Acinetobacter* spp to 1.9% for MDR *Enterobacteriaceae*. Of the 17,677 admissions with a MDR GNB, 1,163 had isolates producing extended-spectrum β-lactamases and 3,054 had isolates that were carbapenem resistant.

Overall, 30.7% of admissions with a subsequent MDR GNB-positive clinical culture had a positive admission MRSA screen (sensitivity) (Table 1; Fig 1). The percentage ranged from 29.8% for MDR *Enterobacteriaceae* to 44.3% for MDR *Acinetobacter*. The percentage increased from 36.3%-54.0% (by species) if patients with an MDRO in the year prior to admission were also included. Of note, 85.5% of admissions without a subsequent MDR GNB-positive clinical culture had a negative admission MRSA screen (specificity).

Table 1
Relationship between MDR GNB clinical culture isolates obtained within 30 days following hospital admission and MRSA polymerase chain reaction nares admission screen or history of positive multidrug-resistant organism* culture within the last year

MDR GNB	Patients with MDR GNB	Patients with MDR GNB and MRSA positive at admission	Patients with MDR GNB and MRSA positive at admission or with history of multidrug-resistant organism* in last 12 months
MDR *Enterobacteriaceae*†	14,607	4,359 (29.8)	5,351 (36.6)
MDR *Pseudomonas aeruginosa*‡	2,761	887 (32.1)	1,077 (39.0)
MDR *Acinetobacter* spp‡	1,141	505 (44.3)	616 (54.0)
Any of above	17,677	5,422 (30.7)§	6,646 (37.6)§

NOTE. Values are n or n (%).
GNB, gram-negative bacteria; *MDR*, multidrug-resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*.
*Including MDR GNB, MRSA, and vancomycin-resistant *Enterococci*.
†Including extended-spectrum β-lactamase and carbapenem-resistant organisms (defined in Methods section).
‡Including carbapenem-resistant organisms.
§Pooled values.

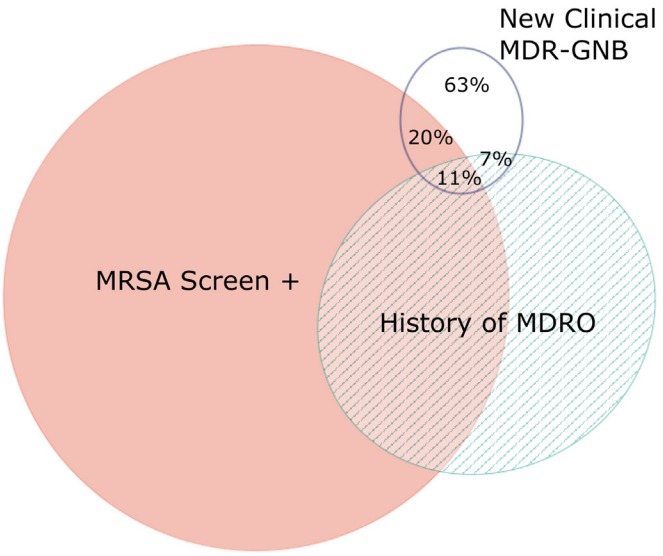

Fig 1. Euler diagram of admissions that have a positive (+) methicillin-resistant *Staphylococcus aureus* (MRSA) polymerase chain reaction hospital admission nares screen, have a history of a clinical multidrug-resistant organism (MDRO) (including MRSA, vancomycin-resistant *Enterococci*, and multidrug-resistant gram-negative bacteria [MDR-GNB]), and have a new clinical MDR-GNB isolated within 30 days following admission to the hospital. Numbers are rounded from actual values.

Table 2
Association between methicillin-resistant *Staphylococcus aureus* polymerase chain reaction nares screen obtained at hospital admission or within 1 year before admission and MDR GNB isolated in a clinical culture within 30 days following admission

MDR GNB	Odds ratio*	95% confidence interval*
MDR *Enterobacteriaceae*†	2.4	2.3-2.5
MDR *Pseudomonas aeruginosa*‡	2.7	2.5-2.9
MDR *Acinetobacter* spp‡	4.3	3.8-4.8
Any of the above	2.5	2.5-2.6

GNB, gram-negative bacteria; *MDR*, multidrug-resistant.
*From generalized linear mixed models (see Methods section).
†Including extended-spectrum β-lactamase and carbapenem-resistant organisms (defined in Methods section).
‡Including carbapenem-resistant organisms.

In a multilevel regression model, admissions with a positive MRSA screen had an odds for a subsequent MDR GNB-positive clinical culture 2.5 times higher than those with a negative MRSA screen (95% confidence interval [CI], 2.5-2.6) (Table 2). The intraclass correlation coefficient, which is the proportion of variance between facilities for this model, was 0.10. In models for specific MDR GNB, the odds ratios were 2.4 (95% CI, 2.3-2.5) for MDR *Enterobacteriaceae*, 2.7 (95% CI, 2.5-2.9) for MDR *P aeruginosa*, and 4.3 (95% CI, 3.8-4.8) for MDR *Acinetobacter* spp.

DISCUSSION

Our analysis demonstrates an association between nasal MRSA carriage at hospital admission and subsequent recovery of MDR GNB from clinical cultures within the next 30 days. The relationship between MRSA nasal carriage at admission and subsequent infection was strongest with *Acinetobacter* spp. Overall, new MDR GNB events may be preceded by nasal MRSA-positive screens or a history of MRSA or clinical MDRO in a substantial proportion of admissions.

Others have shown that patients may be co-colonized with multiple different MDROs, including *Enterobacteriaceae, Acinetobacter* spp, *P aeruginosa*, MRSA, and vancomycin-resistant *Enterococci* in acute and long-term care facilities.[11-19] However, routine admission screening for MDR GNB is generally not performed,[20] and patients carrying these organisms may remain unidentified and not placed in transmission precautions. Our data, taken from a large number of hospitals, suggest carriage of MRSA in the anterior nares may serve as a marker to identify patients with a higher likelihood of harboring MDR GNB. Therefore, when patients are placed in contact precautions because of a positive MRSA screen, there may be a collateral benefit of isolating patients who are at increased risk for transmitting MDR GNB to others within the hospital. Potentially, screening and identification of patients carrying MRSA may have value with respect to reducing exposure to high-risk MDR GNB with minimal or no added cost. In contrast with the conclusions of others, our findings suggest that there may be a beneficial horizontal (across pathogens) effect of an apparent vertical strategy (MRSA screening).[21] This appears to be true in VA facilities which have a high-risk population, documented transmission in the past, and data showing lower transmission of MRSA with universal screening.[1,4] Infection Control personnel at other facilities may wish to adopt universal screening for MRSA as is done in the VA or after assessing their incidence of MDRO HAIs balanced against the potential cost and labor of screening, employ a limited program targeting high-risk patients to gain the potential benefit of early isolation of patients with MDR GNB.

Our data also underscore the value of strict attention to universal infection prevention practices, such as hand hygiene when moving from a known MRSA-positive patient to another MRSA-positive patient, even when they are cohorted in the same room, because each individual may harbor other MDROs. This difference in roommate colonization has been demonstrated previously with MRSA and methicillin-sensitive *S aureus* co-colonization.[22] The current study highlights additional pathogens that may be transmitted between patients if proper cleaning and hand hygiene are not performed. Education of health care workers regarding the risk of transmitting not only MRSA, but also more difficult-to-treat organisms (eg, carbapenem-resistant *Enterobacteriaceae*) could potentially improve compliance with contact precautions and hand hygiene practice. In addition, empirical antibiotic therapy for patients suspected of infection may need to be broader in patients with MRSA, given the higher likelihood of having MDR GNB concurrently, and conversely, could potentially be narrower in patients without MRSA given the high specificity of 85%. Further work using MRSA status as a predictor of MDR GNBs while accounting for factors (eg, intensive care, comorbidities, geographic variation) in resistance prevalence would be of interest for informing stewardship policies on the need for empirical advanced spectrum gram-negative coverage with carbapenems or other agents with activity against MDR GNB.

We acknowledge limitations to our analysis. The VA population is unique (mainly older men) and may not be representative of other populations. Patients colonized with MRSA may also have more comorbidities than those not colonized and be cultured more frequently, thereby increasing the chance of detecting MDR GNB. We surmise that most MDR GNB that were recovered in clinical cultures within 30 days following admission were ones present at the time of admission; however, screening for MDR GNB was not performed. Therefore, we do not know if subsequent recovery of these organisms represented acquisition in hospital. It is possible that patients acquired MDR GNB once admitted because of suboptimal infection control practices. However, if this were the case, it would be difficult to explain why the odds of having MDR GNB were higher in patients in contact precautions for MRSA than in those not in isolation. Another possible limitation of this analysis is that we were unable to determine if the isolates from clinical cultures represented ones that were colonizers or caused infection. In either case, facilities might want to have patients with MDR GNB in contact precautions. Finally, we examined the potential for MDR GNB transmission but not the outcomes of transmission. Ultimately, an assessment on outcomes is necessary. Some studies have addressed this to a limited extent,[23] but our findings suggest that specific pathogens should be investigated (as opposed to any pathogens) because different pathogens appear to have different relationships with MRSA. The strengths of this study include the large national sample size, robust assessment of MRSA nasal carriers, and electronically available national database of all clinical microbiologic cultures.

In conclusion, identification and isolation of MRSA nasal carriers have the potential to result in benefits beyond prevention of transmission and infection with a single organism (MRSA) and may help reduce the spread of MDR GNB. Collateral effects on nontargeted pathogens should be routinely examined in infection control studies targeting specific organisms. Further evaluations of the effectiveness and cost-savings associated with MRSA screening need to take these findings into consideration as a potential added benefit.

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