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Can Nasal Methicillin-Resistant *Staphylococcus aureus* Screening Be Used to Avoid Empiric Vancomycin Use in Intra-Abdominal Infection?

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Abstract

Background: Vancomycin is used widely as empiric therapy for gram-positive organisms in patients with an intra-abdominal infection (IAI), even in those with no history of methicillin-resistant *Staphylococcus aureus* (MRSA) infection or colonization. Potential adverse effects of vancomycin include nephrotoxicity, increased cost, and bacterial resistance. We hypothesized that MRSA nasal screening could be used to predict patients with a MRSA IAI and used to avoid unnecessary empiric vancomycin use.
Methods: A surgical infections database collected prospectively from a single institution was reviewed for all IAIs between January 1, 2000–December 31, 2011. Patients with and without MRSA obtained from abdominal cultures as either a monomicrobial or polymicrobial isolate were compared by univariate analysis. A multivariable logistic regression was performed to identify independent predictors of MRSA IAI.
Results: Of 2,591 patients with an IAI, 240 patients had a nasal MRSA screen within 30 d prior to infection and abdominal culture data, with an incidence of 23% for MRSA IAI. Patients with MRSA IAI (n = 45) had more healthcare associated infections, lower white blood cell counts and greater rates of positive nasal MRSA screenings compared with those with non-MRSA IAI. By multivariable analysis (C statistic = 0.908), the strongest independent predictor of an MRSA IAI was a positive MRSA screen (odds ratio [OR] 40.9, confidence interval [CI] 14.2–118.1). The positive predictive value for a MRSA screen was 53% whereas the negative predictive value of a MRSA screen was 97%.
Conclusion: A negative MRSA nasal screen indicates with near certainty the absence of MRSA as part of an IAI. In the setting of a recent screen, empiric vancomycin can be withheld. Further, rapid MRSA nasal screening could be used to forego or to discontinue vancomycin therapy rapidly in the setting of IAI. This change in empiric antibiotic management of IAI may lead to decreased morbidity, reduction in cost, and a decrease in bacterial resistance.

The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased steadily over the last several decades and has become a threat to both community and hospitalized patients. Such MRSA infections have been associated with increased morbidity and mortality [1–3]. As a result, clinicians are vigilant in their empiric treatment to reduce the morbidity and mortality of an untreated MRSA infection.

The Surgical Infection Society and the Infectious Diseases Society of America have established recommendations to help guide empiric antimicrobial coverage directed against MRSA in intra-abdominal infections [4]. Additionally, vancomycin is recommended for the treatment of suspected or proved intra-abdominal infections because of MRSA [4]. However, the interpretation of these recommendations is often variable and applied inconsistently, with vancomycin often included as empiric treatment in high-risk patients at the physician's discretion.

Vancomycin is currently the antibiotic of choice for serious infections caused by multi-drug resistant gram-positive organisms, such as MRSA, methicillin-resistant coagulase-negative staphylococci, and *Enterococcus faecium* [5]. However, vancomycin is not a benign therapy and the incidence of vancomycin-induced nephrotoxicity varies from 5%–

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35%. Most importantly, vancomycin-resistant strains of bacteria are increasing [5–7] and the excessive use of antimicrobial agents has worsened the susceptibility to vancomycin [8].

Vancomycin is used widely as empiric therapy for gram-positive organisms in patients with an intra-abdominal infection (IAI), even in those with no history of MRSA infection or colonization. This empiric therapy poses substantial morbidity to the patient and society. We hypothesized that nasal MRSA screening could be used to predict patients with MRSA IAI and used to avoid unnecessary empiric vancomycin use.

Patients and Methods

Data source and patient population

Approval for this investigation was obtained from the human investigation committee of the University of Virginia Health System, including a waiver of the need to obtain patient consent. All general surgery, trauma, and transplant patients with an infection at our institution were entered prospectively into the Surgical Clinical Epidemiology Database.

A review was performed of all patients with an IAI from 2000 through 2011. Inclusion criteria included all general surgery, transplant, and trauma patients with an intra-abdominal infection who were 18 y of age or older. All patients were required to have a documented nasal MRSA screen prior to infection. Exclusion criteria included any patient with a MRSA IAI that did not have culture data available or who had a nasal MRSA screen greater than 30 d prior to their infectious period.

Of the 2,591 patients identified with an IAI, 240 patients had a MRSA screen and IAI culture data. These 240 patients were stratified into patients who had a non-MRSA intra-abdominal infection IAI and those had a MRSA IAI.

Variables examined and outcomes measured

An IAI was defined based on U.S. Centers for Disease Control and Prevention criteria and positive culture data. Screening for MRSA was performed by nasal swab and tested with the Xpert (Cepheid, Sunnyvale, CA) polymerase chain reaction (PCR) assay. This assay has a sensitivity of 97% and specificity of 91% [9]. MRSA screening was performed on patients who were admitted to the intensive care unit, transferred from another facility or were hospitalized for greater than one week.

Patient demographic characteristics, comorbidities, hospital risk factors, outcomes and complications were examined. Intra-abdominal infections were defined by their origin (community acquired, hospital acquired, and healthcare associated) and mortality was defined as in-hospital mortality.

The primary endpoint was the occurrence of a MRSA intra-abdominal infection. The influence of peri-infectious parameters on the development of a MRSA IAI were studied.

Statistical analysis

Episodes of infection were analyzed on a per episode basis. Patient demographics, comorbidities, hospital risk factors and hospital complications were compared using a univariate analysis. Categorical variables were compared using the X^2 or Fisher exact test where appropriate. Continuous variables were compared using the Wilcoxon Rank Sum test where appropriate. Categorical data were reported as frequencies and percentages and a statistical significance of $p < 0.05$ was used.

A multivariable logistic regression analysis was performed to model the presence of MRSA and to identify risk factors that are independent predictors of a MRSA IAI. The model was constructed using all available patient data that was significant in the univariate analysis and a backward selection was performed. Odds ratios (OR) and their 95% confidence intervals were computed to assess statistical significance. Subsequently the sensitivity, specificity, negative predictive value, and positive predictive value of a MRSA nasal screen were calculated for a MRSA IAI. All statistical analysis was performed with SAS 9.1.3 software (SAS Institute, Cary, NC).

Results

Between January 1, 2000, and December 31, 2011, there were 2,591 patients with an IAI and a total of 240 patients who had a documented nasal MRSA screen prior to infection and abdominal culture data. Of this cohort 195 patients had non-MRSA IAI and 45 patients had a MRSA IAI.

Patients with and without a MRSA IAI were similar demographically (Table 1). There were no significant differences of age, race, or gender between the two groups. However, patients with a MRSA IAI were more likely to have a positive MRSA screen prior to infection. There was no significant difference in the number of days from nasal MRSA screening to infection between the non-MRSA IAI and MRSA IAI patients. Not surprisingly, non-MRSA IAIs were associated with community-acquired infections,

Table 1. Baseline Demographics in Patients with and without MRSA IAI

	Non-MRSA IAI n = *195*	*MRSA IAI* n = *45*	p*
Age (median) (y)	55 (45–66)	55 (45–59)	0.37
< 65	138	38	0.06
65–74	38	3	0.05
75–84	18	4	0.94
> 85	1	0	1.00
Race			
White	168 (86 %)	39 (87%)	0.93
Black	21 (11 %)	6 (13%)	0.62
Hispanic	3 (1.5%)	0 (0%)	1.00
Other	3 (1.5%)	0 (0%)	1.00
Female	95 (49 %)	24 (53%)	0.58
Origin of infection			
Community acquired	110 (56 %)	16 (36%)	0.01
Healthcare-associated	36 (19 %)	20 (44%)	0.0002
Hospital-acquired	49 (25 %)	9 (20%)	0.47
Positive MRSA screen	34 (17 %)	39 (87%)	< 0.0001
Time from screen to infection (d)	2 (2–14)	0 (0–6)	0.05

*Significance $p < 0.05$

MRSA = methicillin-resistant *Staphylococcus aureus*; IAI = intra-abdominal infection.

Table 2. Comorbidities in Patients with and without MRSA IAI

	Non-MRSA IAI n = *195*	*MRSA IAI* n = *45*	p*
Diabetes mellitus	39 (20%)	15 (33%)	0.05
Coronary artery disease	32 (16%)	6 (13%)	0.61
Peripheral vascular disease	7 (4%)	5 (11%)	0.04
Chronic kidney disease	14 (7%)	6 (13%)	0.18
Chronic pulmonary disease	31 (16%)	10 (22%)	0.31
History of malignant disease	20 (10%)	2 (4%)	0.39
Liver disease	13 (7%)	4 (9%)	0.53
Pre-admission corticosteroid use	46 (24%)	8 (18%)	0.40
Inflammatory bowel disease	16 (8%)	8 (18%)	0.05

*Significance $p < 0.05$

MRSA = methicillin-resistant *Staphylococcus aureus* (MRSA); IAI = intra-abdominal infection.

whereas a MRSA IAI was associated with health care-associated infections. On the other hand, hospital-acquired infections were not significantly different between the groups (Table 1). Diabetes mellitus, inflammatory bowel disease, and peripheral vascular disease were more common in MRSA IAI patients (Table 2).

Patients with a MRSA IAI differed from patients without a MRSA IAI on several hospital-associated risk factors (Table 3). A white blood cell count (WBC) of less than 11×10^9/L was more likely to be associated with MRSA. Conversely, a WBC count of greater than 20×10^9/L was associated with a non-MRSA IAI. Patients with a non-MRSA IAI were more likely to have undergone some type of intra-abdominal intervention within 30 d of the infection episode.

On univariate analysis there was no difference in outcomes (Table 4). Importantly, patients in the MRSA IAI and non-MRSA IAI were not significantly different on acute kidney injury requiring dialysis, length of stay, or in-hospital mortality.

Subsequently, a multivariable logistic regression model was created (C-statistic 0.908, Hosmer-Limeshow goodness-of-fit p 0.306) and several risk factors were found to be associated independently with a MRSA IAI (Table 5). Most importantly, a nasal MRSA screen was found to be an independent predictor of a MRSA IAI with an OR 40.9 (14.2–118.1). Healthcare-associated infection and peripheral vascular disease were associated with a MRSA IAI, whereas a WBC greater than 20×10^9/L was independently associated with non-MRSA IAI.

The calculated sensitivity and specificity of the nasal MRSA swab as a screening tool was 87% and 83%, respectively. The positive predictive value and negative predictive value of the screen were 53% and 97%, respectively.

Discussion

Methicillin-resistant *S. aureus* is one of the most common antimicrobial resistant pathogens, causing invasive infection in both health care settings and in the community [9–11] and is associated with morbidity and mortality [1–3]. Methicillin-resistant *S. aureus* infections occur most commonly in skin/soft tissue and blood stream infections, but can also occur in pneumonia, non-skin abscesses, urinary tract infections, endocarditis, osteomyelitis, and surgical site infections [12].

Although the evidence is limited, a MRSA IAI occurs in approximately 5%–16% of patients [13–15]. The Surgical Infection Society and Infectious Diseases Society of America recommend empiric vancomycin directed against MRSA in patients who have healthcare-associated IAI, are at risk because of prior treatment failure, are at risk because of antibiotic exposure, or in those known to be colonized with MRSA [4]. However, the interpretation of these recommendations is often variable and its implementation can be even more unpredictable. Therefore, determining which patients warrant coverage for MRSA and when to discontinue vancomycin in the absence of a positive culture is a clinical dilemma.

The studies that have reviewed the incidence of MRSA IAI are small in number and nearly a decade old. In a review of

Table 3. Univariate Analysis of Risk Factors For a MRSA IAI

	Non-MRSA IAI n = *195*	*MRSA IAI* n = *45*	p*
Any IAI intervention within 30 d	190 (97%)	40 (89%)	0.01
Post-operative infection	99 (51%)	24 (53%)	0.76
Intensive care unit status	19 (10%)	3 (7%)	0.77
Trauma	7 (4%)	0 (0%)	0.35
Transplant	34 (18%)	5 (11%)	0.30
APACHE II	13 (8–20)	12 (7–17)	0.20
Transfusion	52 (27%)	9 (20%)	0.35
Fever	55 (28%)	10 (22%)	0.42
Tmax	37.6 (37–38.4)	37.4 (37–38.4)	0.72
White blood cell count ($\times 10^9$/L)	14.6 (10–26)	12.3 (9.1–14.8)	0.01
WBC < 11	55 (28%)	22 (49%)	0.01
WBC 11–15	46 (23%)	13 (29%)	0.46
WBC 15–20	43 (22%)	5 (11%)	0.10
WBC > 20	51 (26%)	5 (11%)	0.03

*Significance $p < 0.05$

APACHE = Acute Physiology and Chronic Health Evaluation; MRSA = methicillin-resistant *Staphylococcus aureus* (MRSA); IAI = intra-abdominal infection; WBC = white blood cell count.

Table 4. Post-Infectious Outcomes after a MRSA and Non-MRSA IAI

	Non-MRSA IAI n = *195*	*MRSA IAI* n = *45*	p*
Acute kidney injury-hemodialysis	17 (9%)	2 (4%)	0.54
Respiratory failure-ventilator	30 (15%)	2 (4%)	0.05
Length of stay (d)	13 (6–24)	9 (4–17)	0.09
In-hospital mortality	26 (13%)	4 (9%)	0.62

*Significance $p < 0.05$
MRSA = methicillin-resistant *Staphylococcus aureus* (MRSA); IAI = intra-abdominal infection.

nosocomial infections, *S. aureus* was found to occur in 4%–11% of intra-abdominal infections [13]. In 1999 Fierobe et al. reported a 16% incidence of MRSA IAI in post-operative patients [14]. Methicillin-resistant *S. aureus* has been implicated in surgical site infections, ranging from an incidence of 1.8%–12% [16–18]. In this study, we focused on a ''high risk'' population, patients who were admitted to the intensive care unit, transferred from another facility, or were hospitalized for greater than one week. This ''high risk'' population had a 19% incidence of MRSA IAI.

The association between nasal MRSA colonization and clinical MRSA infection has been demonstrated in hospitalized patients and critically ill patients [19–21]. Furthermore, several studies have looked at the association between MRSA surgical site infection and nasal MRSA colonization. Kalra et al. found that surgical patients with a positive nasal MRSA PCR screen have a nine-fold greater odds of developing a subsequent MRSA surgical site infection compared with those with a negative MRSA PCR screen [17]. Similarly, several other groups reported an independent association between pre-operative nasal MRSA colonization and subsequent MRSA surgical site infection [16,18].

Previously, few have looked at the utility of nasal MRSA screening in predicting MRSA intra-abdominal infection. In post-operative infections, Fierobe et al. reported 12 MRSA IAI out of 73 patients and found MRSA nasal colonization as a risk factor [14]. Similarly, in this study we demonstrated that nasal MRSA colonization is an independent predictor of subsequent MRSA IAI. In a multivariable logistic regression model, a positive nasal MRSA screen increases the risk of a subsequent MRSA IAI by 40-fold. In our cohort the negative predictive value of a nasal MRSA screen for MRSA IAI was significantly high at 97%.

Table 5. Multivariate Logistic Regression Model for Independent Predictors of MRSA IAI

	Wald-Chi Square	p*	*OR 95% CI*
Positive MRSA screen	46.99	< 0.0001	40.9 (14.2–118.1)
Hospital-associated IAI	9.58	0.002	4.6 (1.8– 12.0)
Peripheral vascular disease	5.08	0.02	7.0 (1.3– 37.7)
WBC $> 20 \times 10^9$/L	4.36	0.04	0.3 (0.1– 0.9)

*Significance $p < 0.05$
C-statistic 0.908, Hosmer-Limeshow goodness-of-fit p 0.306
MRSA = methicillin-resistant *Staphylococcus aureus*; IAI = intra-abdominal infection; WBC = white blood cell count; CI = confidence interval; OR = odds ratio.

Our findings have several important implications in the management of patients with IAIs. Our study confirms that a nasal MRSA screen is an important and accurate diagnostic test in patients with an infectious process, particularly in patients with an IAI. In addition, MRSA nasal colonization is an important independent risk factor for a subsequent MRSA IAI.

It is important to consider that the majority of the population is not colonized with MRSA and will not have a MRSA IAI, even in our ''high risk'' population. Many of these patients received empiric treatment with vancomycin because clinicians did not have a tool to identify who would contract a MRSA IAI, or more importantly who would not. In this cohort, 90 patients received vancomycin that were not MRSA colonized and who did not ultimately have a MRSA IAI. The overuse of vancomycin placed these patients at risk for acute kidney injury, had an increased cost, and ultimately added to the overall risk of antibiotic resistance. When used appropriately, a negative nasal MRSA screen indicates with 97% certainty that the patient does not have a MRSA IAI. This can be used as a tool to direct empiric antibiotic therapy and limit vancomycin use.

Limitations

This study is inherently limited by its retrospective nature, however the database utilized was collected prospectively. Of the 2,591 patients with an IAI, only 240 patients had nasal MRSA screening data in addition to IAI culture data. This exclusion may have created a sampling error by limiting the number of patients in the study population. These exclusions may have also introduced bias as nasal MRSA screen was performed on patients who were admitted to the intensive care unit, transferred from another facility or were hospitalized for greater than one week. Lastly, a nasal MRSA screen has limitations as a test with a sensitivity of 97% and specificity of 91%.

Conclusion

A negative MRSA nasal screen indicates with near certainty the absence of MRSA as part of an IAI. In the setting of a recent screen, empiric vancomycin can be withheld. Further, rapid MRSA nasal screening could be used to forego or to rapidly discontinue vancomycin therapy in the setting of an IAI. This change in empiric antibiotic management of IAI may lead to decreased morbidity, reduction in costs, and a decrease in bacterial resistance.

Author Disclosure Statement

No competing financial interests exist.

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