Predictive Value of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Swab PCR Assay for MRSA Pneumonia

Benjamin Dangerfield,[a] Andrew Chung,[b] Brandon Webb,[c] Maria Teresa Seville[d]

Division of Internal Medicine, Maricopa Medical Center, Phoenix, Arizona, USA[a]; Division of Internal Medicine, Mayo Clinic in Arizona, Scottsdale, Arizona, USA[b]; Division of Infectious Disease, University of Utah, Salt Lake City, Utah, USA[c]; Division of Infectious Diseases, Mayo Clinic in Arizona, Phoenix, Arizona, USA[d]

Pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with poor outcomes and frequently merits empirical antibiotic consideration despite its relatively low incidence. Nasal colonization with MRSA is associated with clinical MRSA infection and can be reliably detected using the nasal swab PCR assay. In this study, we evaluated the performance of the nasal swab MRSA PCR in predicting MRSA pneumonia. A retrospective cohort study was performed in a tertiary care center from January 2009 to July 2011. All patients with confirmed pneumonia who had both a nasal swab MRSA PCR test and a bacterial culture within predefined time intervals were included in the study. These data were used to calculate sensitivity, specificity, positive predictive value, and negative predictive value for clinically confirmed MRSA pneumonia. Four hundred thirty-five patients met inclusion criteria. The majority of cases were classified as either health care-associated (HCAP) (54.7%) or community-acquired (CAP) (34%) pneumonia. MRSA nasal PCR was positive in 62 (14.3%) cases. MRSA pneumonia was confirmed by culture in 25 (5.7%) cases. The MRSA PCR assay demonstrated 88.0% sensitivity and 90.1% specificity, with a positive predictive value of 35.4% and a negative predictive value of 99.2%. In patients with pneumonia, the MRSA PCR nasal swab has a poor positive predictive value but an excellent negative predictive value for MRSA pneumonia in populations with low MRSA pneumonia incidence. In cases of culture-negative pneumonia where initial empirical antibiotics include an MRSA-active agent, a negative MRSA PCR swab can be reasonably used to guide antibiotic de-escalation.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as an increasingly important pathogen in pulmonary infection, particularly in patients with significant health care exposure. Guidelines for health care-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) recommend empirical antibiotics targeting MRSA in at-risk patients (1). However, in many cases, cultures are negative and clinicians must determine in whom antibiotics can be safely de-escalated. *S. aureus*, including MRSA, colonizes the nares (2–6), and colonization has been shown to be a predictor of future clinical infection (7–12). MRSA nasal colonization can be accurately detected using the nasal swab PCR test (13, 14). It has been suggested, therefore, that the MRSA PCR nasal swab may be useful as a diagnostic test for patients with infections in whom MRSA is suspected. For this retrospective study, we describe the diagnostic characteristics of the nasal swab MRSA PCR test in predicting culture-confirmed MRSA pneumonia.

MATERIALS AND METHODS

The study was performed at a 244-bed academic tertiary care facility. Heart, kidney, liver, pancreas, and bone marrow transplantation are performed at our institution, but no obstetric or pediatric care is provided. Approval for the study was granted by the Mayo Clinic Institutional Review Board.

Cases were identified by querying the microbiology laboratory database for all patients who underwent nasal swab MRSA PCR testing from January 2009 to July 2011. During this period, routine admission MRSA surveillance was performed at our hospital for select groups only, including stem cell and solid organ transplant recipients and patients admitted with acute leukemia. No routine intensive care unit (ICU) surveillance program was in place during the study period. The majority of MRSA PCR assays reviewed for inclusion in our cohort were ordered for clinical diagnostic purposes in the intensive care unit and for internal medicine patients in the general and intermediate care areas. All PCR testing was performed using the Xpert MRSA (GeneXpert) system (Cepheid, Sunnyvale, CA).

For the same time period, all blood and respiratory cultures (sputum, induced sputum, or bronchoalveolar lavage) were also identified from laboratory records in an identical manner. Because the database was queried for all cultures during the study interval, this list included cultures positive for MRSA, cultures positive for organisms other than MRSA, and cultures with no bacterial growth. These two lists were then cross-referenced against each other to identify only patients who had undergone MRSA PCR testing and from whom a clinical culture specimen had been obtained. Cases were then manually reviewed and included only if they met study criteria for confirmed pneumonia. The case definition for pneumonia was based closely upon other studies in health care-associated pneumonia (15–18): radiographic evidence of infiltrate or cavitation and the presence of two or more of the following clinical signs or symptoms: (i) temperature less than 36.0°C or greater than 38.0°C, (ii) respiratory rate greater than 20, (iii) cough, (iv) hypoxia as evidenced by oxygen saturation less than 90% on room air, (v) increased sputum production, or (vi) a white blood cell count less than 4,000/mm^3 or greater than 10,000/mm^3.

Patients with confirmed pneumonia who had a nasal swab MRSA PCR test and from whom a culture specimen also was obtained were included in the study. Cases were excluded if another diagnosis was more likely than pneumonia and if the nasal MRSA PCR swab was not performed within 1 month prior to clinical culture for patients presenting from the outpatient setting or within 7 days prior to culture results in hospital-

TABLE 1 Patient characteristics

Characteristic	Value for result				No. (%) total
	Positive PCR and positive culture	Positive PCR and negative culture	Negative PCR and negative culture	Negative PCR and positive culture	
No. of patients (all)	22	40	370	3	435
Demographics					
Avg age (yrs)	74.2	72	69.1	79.3	69.7
No. male	12	28	229	3	272 (62.5)
No. female	10	12	141	0	163 (37.5)
No. with pneumonia type					
CAP	7	13	127	2	149 (34.3)
HCAP	13	25	200	0	238 (54.7)
HAP	2	2	43	1	48 (11.0)
Level of care					
Medical/surgical unit	13	25	214	2	254 (58.4)
Intermediate/ICU	9	15	156	1	181 (41.6)
Antibiotic coverage					
Empirical MRSA-active antibiotics given	17	22	203	1	243 (55.9)
% of empirical MRSA coverage	77.3	55.0	54.9	33.3	

acquired cases. These cutoffs were chosen based upon studies indicating that colonization status in outpatients does not fluctuate rapidly in the absence of significant MRSA exposure (19, 20) and studies by Byrnes et al. (10) and Sarikonda et al. (12) suggesting that colonization status for inpatients can change within as few as 7 days from initial testing. The majority (>80%) of culture specimens were obtained within 48 h of the MRSA swab.

Data abstracted from the electronic medical record included age, gender, type of pneumonia according to the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines (CAP, HCAP, or HAP [1, 21]), level of medical care (general medical/surgical ward versus intermediate or intensive care unit), and use of empirical antibiotics directed against MRSA. Empirical antibiotics were defined as antibiotics administered within 8 h of admission for new admissions or the initial empirical regimen administered when HAP or VAP was suspected. The majority of MRSA PCR swabs were collected at the time of diagnosis of pneumonia, at or near the time of clinical culture collection and antibiotic administration. However, time stamp data from the electronic medical record was not accurate enough to determine whether the swab was collected prior to administration of anti-MRSA antibiotics.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the MRSA nasal swab for detecting culture-proven MRSA pneumonia were calculated. Ninety-five percent confidence intervals were calculated according to the efficient-score method, corrected for continuity (22). Calculations were performed using a Web-based statistical software package (VassarStats [www.vassarstats.net]; accessed 14 June 2012).

RESULTS

During the study period, 2,740 patients had nasal swab MRSA PCR testing. Of the patients with nasal swabs, 696 had at least one blood or respiratory bacterial culture performed. Two hundred sixty-one patients were excluded because the duration of time between the MRSA nasal swab and pneumonia exceeded predefined limits ($n = 87$) or because another diagnosis was more likely than pneumonia ($n = 174$).

Four hundred thirty-five patients were included in the final analysis (Table 1). Average patient age was 69.7 years, and 62.5% were male. Sixty-two of 435 (14.3%) MRSA nasal swabs were positive. For 25 of 435 patients, cultures were positive for MRSA (23 sputum and 2 blood samples), resulting in a prevalence of MRSA infection of 5.7% in our cohort. Most cases were classified as HCAP (54.7%), with CAP and HAP comprising 34.3% and 11.0% respectively. There were only 3 patients who met criteria for ventilator-associated pneumonia (VAP). Because of the limited number of VAP cases, these cases were included in HAP for analysis. Fifty-eight percent of patients were treated on the medical floor, and 41.6% were treated in the intermediate care or intensive care unit.

The nasal swab MRSA PCR test demonstrated the following diagnostic performance characteristics for detecting culture-proven MRSA: sensitivity, 88.0%; specificity, 90.1%; positive predictive value (PPV), 35.4%; and negative predictive value (NPV), 99.2%. The NPV of the MRSA nasal swab for MRSA HCAP was 100.0%, for that for CAP was 98.4%, and that for HAP was 97.7%.

Slightly more than half (55.9%) of all patients received empirical MRSA-active antibiotics, and 72.0% of the patients with culture-positive MRSA pneumonia received empirical therapy targeting MRSA. There was no statistical difference in the 30-day mortality (0 deaths versus 3 deaths) or the duration of hospitalization (4.7 and 6.9 days) between those treated with empirical MRSA antibiotics and those that were not ($P = 0.40$ and 0.32, respectively). Complete results are in Tables 1 to 4.

DISCUSSION

When implicated as a primary pathogen in lower respiratory tract infection, MRSA is associated with significant morbidity and mortality (23, 24). This is particularly true when appropriate antibiotic therapy targeting MRSA is not included in an initial empirical regimen. However, determining which patients warrant anti-MRSA coverage, and once that is initiated, when it is safe to narrow the antibiotic spectrum in the absence of positive cultures represents a clinical dilemma.

TABLE 2 MRSA swab PCR results

| MRSA swab PCR result | No. (%) of cases with culture result[a] | | Total swabs |
	Positive for MRSA	Negative for MRSA	
Positive swab	22[a]	40[b]	62 (14.3)
Negative swab	3[c]	370[d]	373 (85.7)
Total cultures	25 (5.7)	410 (94.3)	435

[a] Specimens collected: sputum, 18 cases; blood, 1 case; bronchoalveolar lavage (BAL), 2 cases; pleural plus BAL, 1 case.
[b] Specimens collected: sputum, 1 case; blood, 25 cases; blood plus sputum, 9 cases; blood plus BAL, 4 cases; blood plus pleural, 1 case.
[c] A sputum sample was collected for each of the 3 cases.
[d] Specimens collected: 17 sputum, 17 cases; blood, 180 cases; BAL, 2 cases; blood plus sputum, 112 cases; blood plus BAL, 30 cases; blood plus pleural, 12 cases; sputum plus BAL, 5 cases; sputum plus pleural, 1 case; blood plus sputum plus BAL, 5 cases; blood plus sputum plus pleural, 5 cases; blood plus BAL plus pleural, 1 case.

One barrier to accurate prediction is that the incidence of MRSA pneumonia appears to vary significantly with individual patient risk factors and local epidemiological patterns. In one large cohort from 162 hospitals in the United States, 8.9% of all culture-positive cases of CAP, 26.5% for HCAP, and 22.9% for HAP were attributable to MRSA (25), and similar rates have been reported from other large centers (17). Other studies, however, suggest much lower rates, with reported prevalences of <0.6 to 0.9% for CAP (16, 26–29) and 2% to 3.5% for HCAP (16, 26, 29). In our cohort, the overall prevalence of MRSA pneumonia was 5.7%, including a 6.0% rate among cases of CAP (9/149), 5.5% for HCAP (13/238), and 6.3% for HAP (3/48).

Nasal colonization with MRSA has been well established as a risk for subsequent clinical MRSA infection (2, 9, 30–34). In 2004, the National Nosocomial Infections Surveillance System reported a rate of MRSA colonization of 1.5% (7). This rate is higher among patients admitted to the hospital (3.4%) (2), those admitted to the ICU (21.9%) (12), and health care workers (4 to 15%) (35, 36). The prevalence of nasal MRSA colonization in our hospital is 5 to 7%. In our cohort of pneumonia patients, however, the overall rate of nasal colonization was 14.3% (62/435). Most studies have suggested that the duration of colonization appears to be about 1 year (19, 20), although some patients remain colonized for much longer periods (37). Those colonized by MRSA have been found to have a significantly increased risk of MRSA infection in the immediate hospitalization and the year following (2, 9, 30–34, 38). In patients with colonization lasting more than 1 year, the rate of subsequent clinical infection has been estimated at 23% (38).

Although multiple studies have attempted to determine the utility of the MRSA nasal swab for predicting MRSA infection,

TABLE 3 Statistical analysis

Test characteristic	Result	95% confidence interval
Sensitivity (%)	88.0	67.6–96.9
Specificity (%)	90.1	86.6–92.8
Positive predictive value (%)	35.4	24.0–48.7
Negative predictive value (%)	99.2	97.4–99.8
Positive likelihood ratio	8.9	6.4–12.3
Negative likelihood ratio	0.1	0.05–0.39

TABLE 4 Analysis by pneumonia type

| Pneumonia type(s) (n^a) | Test efficacy | | | |
	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
All (435)	88.0	90.1	35.4	99.2
CAP (149)	77.8	90.7	35.0	98.4
HCAP (238)	100.0	88.9	34.2	100.0
HAP (48)	66.7	95.6	50.0	97.7

[a] n, total no. of patients.

significant heterogeneity exists with regard to the use of PCR versus chromogenic culture medium, body site sampled for colonization, and timing (8, 11, 12, 39, 40). The two largest of these studies, a retrospective review by Robicsek et al. (11) and a prospective analysis by Harris et al. (8), both suggest that the nasal MRSA PCR (GeneOhm; Becton, Dickinson and Company) demonstrates a modest PPV but an NPV greater than 98% for MRSA infection at any body site. In subgroup data analysis of 426 patients with respiratory specimens, Robicsek et al. reported an NPV of 98%; the prevalence of MRSA infection in this group was 5.6%. In contrast, in a prospective study of 1,083 ICU patients using the same PCR-based assay, Sarikonda et al. found that surveillance MRSA nasal swab PCR screening on admission had a sensitivity of 24.2%, specificity of 78.5%, PPV of 17.7%, and NPV of 84.4% for MRSA lower respiratory infection (12, 41).

In our cohort, the overall NPV of the MRSA nasal swab PCR for MRSA infection was excellent at 99.2%, while the PPV was 35.5% when the test was used in the diagnosis of pneumonia. Similar results were observed when the test was applied to each of the three categories of pneumonia. The diagnostic performance was best in the HCAP group, where an NPV of 100% was calculated. These results are consistent with those of larger studies, which suggest that, as with MRSA infection at other body sites, determination of MRSA colonization is useful in the evaluation of suspected respiratory infection due to MRSA. The modest differences in performance of the MRSA PCR in our cohort compared to that in the Sarikonda study are likely related to underlying factors impacting the prevalence of MRSA in the two populations. Both the prevalence of MRSA colonization (24.4% versus 14.3%) and infection (21.9% versus 5.7%) were much higher in the Sarikonda group, contributing to a lower NPV. In addition, only 43% of patients in our group were treated in the ICU or intermediate care unit, of which less than 2% had ventilator-associated pneumonia (VAP).

Our findings have several important implications for antimicrobial stewardship. First, our experience suggests that clinicians remain unsure when to initiate empirical MRSA coverage. In our cohort, 56% of patients received initial empirical antibiotics with activity against MRSA, including only 72% of patients who were ultimately diagnosed with MRSA pneumonia. Current ATS/IDSA guidelines for CAP and HCAP recommend therapy targeting MRSA if risk factors, such as cavitating pneumonia, end-stage renal disease, injection drug abuse, prior influenza, and prior antibiotic therapy, are present or if local prevalence is high (1, 21). The HCAP category itself was originally proposed as a method for identifying multidrug-resistant pathogens, including MRSA, in

patients with pneumonia. However, the positive predictive value of the HCAP criteria for MRSA pneumonia in highly MRSA-prevalent (14%) populations is only 26.5% (25) and is as low as 3.6% in low-prevalence settings (29).

Additional risk factors for MRSA pneumonia, including fever of >39.0°C, hemoptysis, leukopenia, MRSA colonization, frequent skin/soft tissue infection, chronic obstructive pulmonary disease (COPD), tobacco use, recent hospitalization, HIV infection, and liver disease, have been identified in other studies (42, 43). However, in isolation each of these factors lacks sensitivity and specificity, and none have been studied in combination. Recently Shorr et al. derived the following clinical prediction score for MRSA pneumonia from a relatively high-prevalence (14%) cohort: two points for recent hospitalization and one point each for an age of <30 or >79, prior intravenous (i.v.) antibiotic exposure, dementia, cerebrovascular disease, status as a diabetic female, or recent stay in a long-term residence facility (44). At scores of 0 or 1, the model identified patients with a <10% risk of MRSA (PPV = 19.6%; NPV 90.1%), while the prevalence of MRSA pneumonia increased to >30% with scores of ≥6. Interestingly, even in our relatively low-prevalence cohort, the positive predictive value of the MRSA PCR nasal swab was superior to that of any of the screening methods described above. While this test cannot be advocated as a diagnostic modality based on these results, further research may be warranted to evaluate the possible additive benefit of combining clinical prediction models and the MRSA PCR assay.

In clinical practice, empirical anti-MRSA agents are increasingly included in the initial empirical regimen, and in culture-negative cases, safe and appropriate de-escalation poses an additional challenge. Recently, Boyce et al. described the successful implementation of an MRSA screening strategy to assist in de-escalation (45). For 91 patients admitted with HCAP, in-hospital mortality was no different following discontinuation of MRSA-active therapy if nasal and throat swabs cultured on chromogenic MRSA agar were negative and if the modified clinical pulmonary infection score (CPIS) was ≤6. Given the robust NPV of the MRSA PCR test in our cohort, which included a large subset of patients meeting HCAP criteria, our results suggest that MRSA PCR testing can be an important tool to guide antibiotic de-escalation following empirical anti-MRSA therapy. In areas with high baseline MRSA prevalence or in individual patients for whom pretest probability of infection is high, coupling the MRSA PCR nasal swab to a clinical prediction rule, such as a Shorr MRSA score of ≤1 or CPIS of ≤3, may augment the negative predictive value. This remains to be evaluated.

Limitations of this study include its retrospective design, which precluded more rigorous control of such variables as timing of MRSA swab collection and standardization of culture work-up. It is conceivable that in some cases, administration of MRSA-active agents prior to collection for MRSA PCR could have contributed to false-negative testing or conversely obscured clinical cultures leading to false-positive results. Many (70.2%) of the respiratory cultures were performed with sputum specimens (Table 2), which differentiate upper respiratory tract colonization from lower-tract pathogens less accurately than do cultures collected via bronchoscopy. In addition, only swabs of the nares were obtained, which may have limited the diagnostic yield of our assay. Some studies have demonstrated that swabbing both the nares and the throat

may increase the sensitivity of MRSA screening (45). Indeed, this may offer a possible explanation for the 3 cases in our study in which nasal swab testing was negative but sputum cultures were positive (false-negative results). Last, the overall prevalence of MRSA pneumonia in this study was average by national standards at 5.7%. Our results may not be generalizable to centers with a substantially higher prevalence of MRSA or individual patients with risk factors that convey a high pretest probability of MRSA infection.

Conclusion. The results of this retrospective analysis suggest that in patients with pneumonia, the nasal swab MRSA PCR test has a mediocre positive predictive value but an excellent negative predictive value for MRSA in centers with a moderate background prevalence of MRSA pneumonia. A potentially important clinical implication of these results is that for patients treated empirically with antibiotics with MRSA activity, a nasal swab negative for MRSA by PCR can be reasonably used to guide antibiotic de-escalation provided that the pretest probability of MRSA pneumonia is not extremely high. A prospective trial is needed in order to confirm these findings.

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