Revised: 22 February 2021 | Accepted: 28 March 2021

DOI: 10.1111/tid.13612

ORIGINAL ARTICLE

WILEY

Utility of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening in patients with acute myeloid leukemia (AML)

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Abstract

Background: Current literature has demonstrated the utility of the MRSA nasal screen as a de-escalation tool to decrease unnecessary anti-MRSA antibiotic therapy. However, data on the applicability of this test in patients with hematologic malignancy is lacking.

Methods: This is a single-center, retrospective cohort study of patients with acute myeloid leukemia (AML) with or without a history of hematopoietic cell transplant (HCT), with pneumonia and MRSA nasal screening with respiratory cultures obtained. The primary outcome was to determine the negative predictive value (NPV) of the MRSA nasal screen for MRSA pneumonia. Secondary outcomes included sensitivity, specificity, positive predictive value (PPV) of the MRSA nasal screen and prevalence of MRSA pneumonia.

Results: Of 98 patients with AML and pneumonia, the prevalence of MRSA pneumonia was 4.1% with confirmed positive MRSA respiratory cultures observed in 4 patient cases. In patients with confirmed MRSA pneumonia, 3 had positive MRSA nasal screens while 1 had a false negative result, possibly due to a long lag time (21 days) between MRSA nasal screen and pneumonia diagnosis. Overall, the MRSA nasal screen demonstrated 75% sensitivity and 100% specificity, with a PPV of 100% and a NPV of 98.9%.

Conclusions: Given the low prevalence, empiric use of anti-MRSA therapy in those AML and HCT patients with pneumonia may not be warranted in clinically stable patients. For patients in whom empiric anti-MRSA antibiotics are initiated, nasal screening for MRSA may be utilized to de-escalate anti-MRSA antibiotics in patients with AML with or without HCT.

KEYWORDS

acute myeloid leukemia, antimicrobial stewardship, hematopoietic cell transplant, methicillin-resistant *Staphylococcus aureus*, pneumonia, predictive values, prevalence, sensitivity, specificity

1 | INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia remains uncommon in the United States, nevertheless, the use of empiric anti-MRSA antibiotics in the setting of pneumonia remains prevalent. According to a multicenter prospective active surveillance study of patients with community-acquired pneumonia (CAP), only 1.6% of the 2,259 patients were demonstrated to be caused by *S aureus*, with only 0.7% MRSA. Despite this low rate, 29% of patients received empiric anti-MRSA antibiotic therapy.[1] In patients with healthcare-associated pneumonia (HCAP), the rate of MRSA pneumonia is also low, at approximately 1%-6.3%.[2-7] IDSA guidelines recommend initiation of anti-MRSA antibiotic therapy for patients with high MRSA risk, including patients with CAP and previous isolation of MRSA or patients with severe CAP with recent hospitalization and parenteral antibiotics within 90 days, patients with ventilator-associated pneumonia (VAP) in units with >10%-20% of MRSA isolates, patients with hospital-acquired pneumonia (HAP) in units with >20% of MRSA isolates, patients with HAP or VAP who are hospitalized in units with unknown MRSA prevalence, patients with HAP or VAP and prior intravenous antibiotic use within 90 days, and patients with HAP and high mortality risk such as those requiring ventilator support or who are in septic shock. These guidelines also prompt clinicians to discontinue therapy as soon as possible in order to decrease potential unwarranted adverse reactions from therapy, minimize healthcare costs, and limit the development of bacterial resistance.[8,9] However, de-escalating antibiotics, even in the improved patient, can be challenging due to limitations in obtaining adequate respiratory cultures and the increased time to await culture growth.

The use of MRSA nasal screen may help aid clinicians in antibiotic de-escalation due to rapid detection and a negative predictive value (NPV) for MRSA pneumonia of greater than 95%.[6,10-13] Unfortunately, most literature for the utility of MRSA nasal screening for antibiotic de-escalation has been primarily in intensive care units (ICU) and general medicine patients, limiting the external validity to other patient populations.[6,10-13] Data are limited regarding the use of MRSA nasal screen in patients with acute myeloid leukemia (AML) with or without hematopoietic cell transplant (HCT). Thus, our study aims to evaluate the prevalence of MRSA pneumonia in this patient population and assess the utility of MRSA nasal screening for anti-MRSA antibiotic de-escalation.

2 | PATIENTS AND METHODS

2.1 | Study setting and subjects

A retrospective cohort study was conducted at Michigan Medicine (MM), Ann Arbor, MI, a 1,000-bed tertiary care university-affiliated hospital. The study was approved by the Institutional Review Board (IRB) at MM (approval number HUM00170574) and written informed consent was waived by the IRB given the retrospective nature of the study.

Adults (≥18 years of age) with AML and a diagnosis of pneumonia who underwent MRSA nasal screening from July 1, 2014 to October 1, 2019 were identified via the electronic medical record (Michigan Medicine Data Direct) and screened for inclusion in the study. Patients were excluded if they did not meet clinical criteria for pneumonia, if they did not have respiratory cultures pertaining to their pneumonia diagnosis, if they received MRSA active antibiotics for ≥48 hours within 30 days prior to the MRSA nasal screen, or if MRSA nasal decolonization was conducted within 30 days prior to the MRSA nasal screen. For patients with multiple MRSA nasal screens, the most recent nasal screen correlating to pneumonia diagnosis was used for analysis as long as no exclusion criteria were met. During the study period, a routine MRSA nasal screen was performed on admission for all patients admitted to hematology/oncology units at Michigan Medicine.

2.2 | Study definitions

To fulfill the criteria for pneumonia in this study, all of the following parameters had to be met: (1) radiographic evidence with either a chest X-ray or computed tomography, (2) presence of ≥2 clinical signs or symptoms, and (3) decision to treat. Clinical signs or symptoms were defined as: (i) new or increasing cough, (ii) purulent sputum or change in sputum, (iii) new or increased dyspnea, (iv) hypoxemia, (v) auscultatory findings, (vi) temperature ≤36°C or ≥38°C, or (vii) WBC >10,000/mm^3 or <4,000/mm^3 or bands >15%. Definitions of CAP or HAP were based on the ATS/IDSA guidelines.[8,9] MRSA active antibiotics included clindamycin, linezolid, tetracyclines, rifampin, trimethoprim-sulfamethoxazole, daptomycin, tigecycline, and vancomycin.

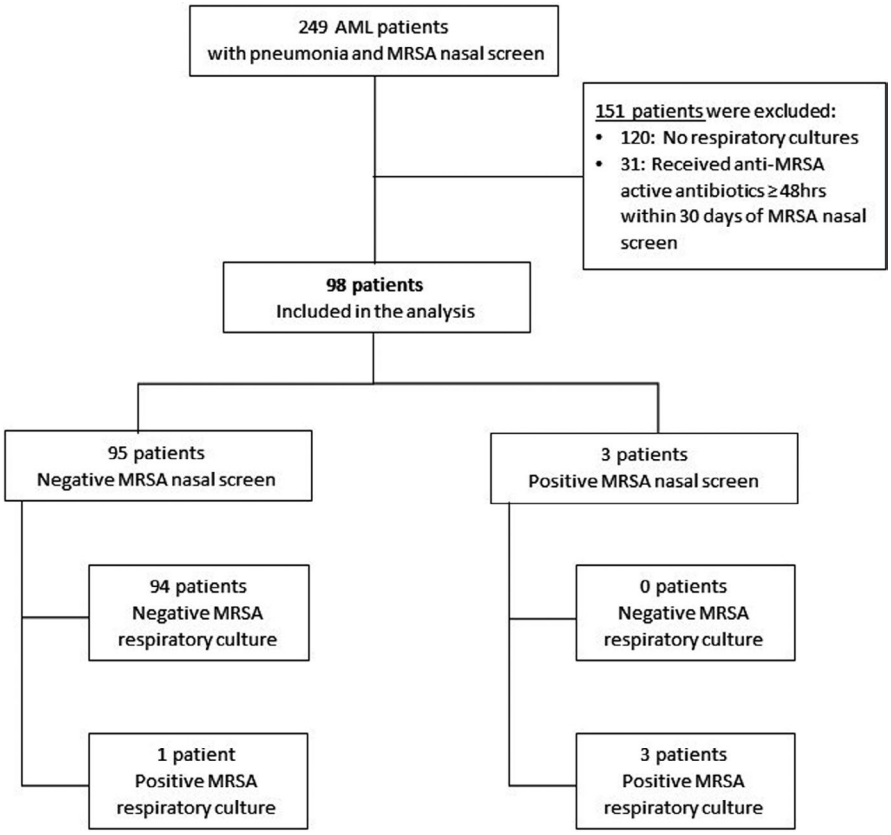
2.3 | Statistical analysis

Descriptive statistics were used to describe the characteristics of the study population. Continuous variables were reported as median with interquartile range. Categorical variables were reported as the percentage of the study population or parameter being assessed. Standard formulas were used to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and prevalence. Statistical analysis was performed using SPSS software (SPSS).

3 | RESULTS

A total of 249 AML patients with MRSA nasal screen and pneumonia were screened for inclusion of which 98 patients were included for analysis (Figure 1). The most common reason for exclusion was the absence of respiratory cultures (120 patients). Thirty-one additional patients were excluded due to the use of anti-MRSA antibiotics within 30 days of the MRSA nasal screen. The majority of

FIGURE 1 Patient flow diagram



subjects were male (66.3%, n = 65) and median age was 61 years (range 23-80 years). There was a comparable amount of CAP (51%, n = 50) cases as there were HAP (49%, n = 48) cases. The median length of stay in the hospital was 24 days while the median length of stay from admission to pneumonia diagnosis was 2 days. The majority of AML patients were newly diagnosed (39.8%, n = 39), while 32.7% (n = 32) were relapsed/refractory and 27.5% (n = 27) were in remission. Of these patients, 90.8% (n = 89) had a history of chemotherapy and 41.8% (n = 41) had a history of HCT prior to study inclusion. Additional baseline demographics are listed in Table 1.

Of the 98 patients included, only 3 patients had a positive MRSA nasal screen, obtained a median of 1 day (range 0-31days) prior to pneumonia diagnosis (Table 2). As shown in Table 3, sputum cultures (87.4%, n = 83) were the most common respiratory cultures obtained. Positive respiratory cultures (any organism) were observed in 28.6% (n = 28) of patients. The prevalence of MRSA pneumonia was 4.1% (n = 4). Three of the four patients with MRSA pneumonia had positive MRSA nasal screens. The diagnostic performance characteristics of the MRSA nasal screen in detecting MRSA pneumonia were: sensitivity, 75%; specificity, 100%; positive predictive value (PPV), 100%, and negative predictive value (NPV), 98.9%.

Concomitant blood cultures were obtained in 94.9% (n = 93) of the study population. Overall, 2 (2.1%) patients had blood cultures positive for MRSA; both of these patients also had respiratory cultures positive for MRSA.

Seventy-nine percent (n = 77) of the study population received empiric anti-MRSA antibiotics for pneumonia, and 95% of those (n = 73) had respiratory cultures that did not grow MRSA. The median duration of anti-MRSA antibiotics for patients with negative MRSA respiratory cultures was 1 day (range of 1-7 days), and 27% (n = 20) received therapy for at least 3 days.

4 | DISCUSSION

MRSA pneumonia has a high rate of morbidity and mortality, especially if empiric.

anti-MRSA antibiotic therapy is not administered.[14-16] However, the prevalence of MRSA pneumonia remains low at ≤10%.[1,6,7,17-19] In a meta-analysis of 22 studies, the rates of MRSA pneumonia ranged from <1% to 56%, with higher numbers attributed to possible selection bias. This analysis reported a pooled prevalence rate of 10%.[19] Similarly, most studies in HCT demonstrated that although pneumonia is a frequent infection (incidence rate of 15%-30%), especially if accompanied by GVHD, *S aureus* is rarely the causative organism.[20-23] For instance, a multicenter Spanish Network of Infection in Transplantation (RESITRA) study found only 2 cases of *S aureus* pneumonia among a cohort of 427 allogeneic HCT recipients.[23]

Despite these findings, the use of empiric anti-MRSA active antibiotics remains high. Accordingly, our study in patients with AML with or without HCT demonstrated a high utilization of empiric anti-MRSA active antibiotics for pneumonia (79%) despite a low prevalence (4.1%) of MRSA pneumonia. A retrospective study conducted by the Veterans Health Administration health care system demonstrated that patients with CAP who received empiric anti-MRSA active antibiotic with standard antibiotic therapy (adjusted risk ratio

TABLE 1 Baseline demographics

Characteristic	n = 98
Age (median [IQR])	61 (53-69)
Gender (no [%])	
Male	65 (66.3)
Female	33 (33.7)
History of positive MRSA nasal screen[a] (no [%])	1 (1)
Type of PNA (no [%])	
CAP	50 (51)
HAP	48 (49)
Duration of hospitalization in days from admission to PNA diagnosis (median [IQR])	2 (15)
Duration of hospitalization in days (median [IQR])	24 (9-37)
Charlson Comorbidity Index (median [IQR])	7 (6-10)
Neutropenia (ANC <1500)[b] (no [%])	59 (60.2)
Duration of neutropenia in days[b] (median [IQR])	13 (6-23)
Disease status (no [%])	
Newly diagnosed	39 (39.8)
Relapsed/Refractory	32 (32.7)
Remission	27 (27.5)
History of chemotherapy (no [%])	89 (90.8)
Chemotherapy regimen[c] (no [%]), n = 89	
3 + 7	12 (13.5)
FLAG	37 (41.6)
Decitabine ±venetoclax	8 (8.9)
MEC	3 (3.4)
Clofarabine based	3 (3.4)
HiDAC based	13 (14.6)
Others	13 (14.6)
Time from most recent chemotherapy to study inclusion in days (median [IQR])	18 (8-195)
History of HCT (no [%])	41(41.8)
Conditioning regimen (no [%]), n = 41	
Myeloblative	38 (92.7)
Non-myeloblative	3 (7.3)
Time from most recent HCT to study inclusion in days (median [IQR])	504 (171-1403)
Current GVHD (no [%]), n = 41	31 (31.6)
Type of GVHD (no [%]), n = 31	
Acute	8 (25.8)
Chronic	28 (90.3)

Abbreviations: CAP, community-acquired pneumonia; GVHD, graft-versus-host disease;HAP, hospital-acquired pneumonia; HCT, hematopoietic cell transplant; MRSA, methicillin-resistant *Staphylococcus aureus*; PNA, pneumonia.

[a]History ≤90 days of study inclusion.

[b]From pneumonia diagnosis to discharge date.

[c]Most recent chemotherapy regimen prior to study inclusion.

TABLE 2 Comparison of results: MRSA nasal screen and respiratory cultures

Respiratory Cultures			
Nasal Cultures	**MRSA positive**	**MRSA negative**	**Total**
MRSA positive	3	0	3
MRSA negative	1	94	95
Total	4	94	98

TABLE 3 Microbiologic data

Parameter	n = 98
MRSA nasal screen (no [%])	
Positive	3 (3.1)
Negative	95 (96.9)
Type of respiratory culture (no [%])	
Sputum	83 (87.4)
Tracheal aspirate/endotracheal tube	15 (15.8)
BAL	24 (25.3)
Respiratory culture result (no [%])	
Positive MRSA	4 (4.1)
Positive Other/s	24 (24.5)
Negative	70 (71.4)
Blood culture (no [%])	93 (94.9)
Blood culture results (no [%]), n = 93	
Positive MRSA	2 (2.1)
Positive Other/s	29 (31.2)
Negative	62 (66.7)

Abbreviations: BAL, bronchoalveolar lavage; MRSA, MRSA, methicillin-resistant *Staphylococcus aureus*; RPAN, respiratory panculture.

[aRR], 1.4 [95% CI, 1.3-1.5]) or without standard antibiotic therapy (aRR, 1.5 [95% CI, 1.4-1.6]) had an increased 30-day all-cause mortality compared to standard antibiotic therapy alone. Additionally, adverse outcomes such as the development of acute kidney injury and secondary infections (*Clostridioides difficile*, vancomycin-resistant *Enterococcus* spp. or gram-negative bacilli) were associated with those who received empiric anti-MRSA active antibiotics with standard antibiotic therapy compared to standard antibiotic therapy alone.[24] This illustrates the pressing need for better guidance and risk stratification in the selection of empiric anti-MRSA antibiotics for patients with pneumonia.

Current guidelines suggest administering empiric anti-MRSA antibiotics for patients with clinical risk factors. However, formal recommendations for de-escalation have not been established, which often leads to prolonged, unnecessary anti-MRSA antibiotic therapy. Although the median duration of empiric anti-MRSA antibiotics in this cohort was only 1 day, 27% of patients without MRSA pneumonia received anti-MRSA antibiotics for a duration of ≥3 days. The relatively

rapid de-escalation in the majority of patients in our cohort is likely a reflection of integrated clinical pharmacist specialist support on all hematology/oncology services at our institution. In other cohort studies, improper antibiotic use has been reported to be as high as 50%, which can lead to undesirable outcomes including medication-related adverse events, *C difficile* infection, increased expense, and antimicrobial resistance.[25-27] Positive outcomes have been demonstrated with implementation of active MRSA nasal surveillance programs. For instance, a pharmacist-driven interventional study by Baby et al led to a reduction of MRSA active antibiotics by approximately 2 days and a lower incidence of acute kidney injury.[28] Another study of utilizing MRSA nasal screen for vancomycin de-escalation in ICU patients demonstrated a total cost savings of $108 per patient.[29]

The routine use of MRSA nasal screen for de-escalation of anti-MRSA antibiotic therapy for patients with pneumonia has been used in various hospital settings due to its robust NPV.[12,13,28-30] A 96.5% NPV was reported in the previously aforementioned meta-analysis and is in concordance with various retrospective studies (>95%), including ours, which demonstrated an NPV of 98.9%.[6,10-13,19] A high NPV suggests that a negative MRSA nasal screen can be used as an excellent surrogate marker to rule out MRSA pneumonia, thus, it may be utilized as a de-escalation tool for anti-MRSA antibiotics prior to availability of respiratory culture results in AML and HCT patients. Over half of our patients (60%, n = 59) were neutropenic, 42% had a history of HCT, and 32% (n = 31) had concurrent GVHD at the time of pneumonia diagnosis (76% of the HCT population). These characteristics are similar to patients in the aforementioned RESITRA study, which found HCT patients with a history of GVHD had a higher risk of pneumonia.[23] Altogether, it is reassuring that such an assay can be applied accurately in high-risk AML and HCT patients at risk for acquiring antimicrobial-resistant organisms.

Of note, one patient in our study had a negative MRSA nasal screen whose subsequent respiratory culture and blood culture were MRSA positive. This patient's MRSA nasal screen was obtained on the 1st day of admission, and the patient developed MRSA pneumonia 21 days after hospitalization. No additional MRSA nasal screens were completed after the initial admission screen, and the disparity between MRSA nasal screen and respiratory culture could be due to the extended time between the MRSA nasal screen and respiratory culture. Colonization may have occurred in the 21-day interval, thus a nasal screen obtained concurrently with pneumonia onset may have been informative. A retrospective review of the utility of MRSA nasal screens in ICU patients for predicting positive MRSA cultures found that sensitivity was significantly higher for nasal screens obtained within 6 days of clinical culture (sputum, blood, incision, and urine) compared to those obtained seven days or more from obtaining cultures.[31] Accordingly, a systematic review by Smith, et al had proposed a 7-day cut-off between nasal MRSA screen and respiratory culture to guide clinicians for anti-MRSA antibiotics de-escalation based on the limited data available.[10]

Similar to other studies that describe the validity of MRSA nasal screens, our sensitivity was low at 75% while specificity was high at 100%. However, our PPV of 100% differs from the PPV seen in other studies, which are generally <50%.[6,10-13,19] Both NPV and PPV are related to the prevalence of the disease state being analyzed (in this case MRSA pneumonia). A high PPV suggests a high likelihood of MRSA pneumonia in patients with the positive nasal screen. In our study population, all patients (3/3) who had positive MRSA nasal screens resulted in a positive respiratory culture, thus giving our study a higher PPV than what has been previously reported. This high PPV is likely attributed to our smaller sample size with a very low number of positive MRSA nasal screens (3/98).

The majority of studies demonstrating a high NPV (≥95%) of MRSA nasal screens were from institutions with a low prevalence of MRSA pneumonia (<10%), similar to ours. Thus, it is important to consider that facilities or units with a higher prevalence of MRSA pneumonia may not match this NPV.[10,19,32] As previously mentioned, both PPV and NPV are affected by prevalence, in which prevalence has an inverse relationship with NPV. In a study by Sarikonda et al of ICU patients with an MRSA prevalence of 23.8%, the reported NPV was lower (84.4%).[32] However, it is important to note that nasal screens were only obtained in 69% of the ICU population, and the time between MRSA nasal screen and culture results were not specified which may have skewed the results. Of note, other ICU studies with MRSA prevalence rates of 10.5%, 10.7%, and 17.9% demonstrated higher NPV results of 98.6%, 94%, and 89.57%, respectively.[30,33,34] Therefore, caution should be exercised in extrapolating these results to populations with a higher MRSA prevalence and further research is required in this area.

Limitations of the present study include its smaller sample size and retrospective study design in which various variables that may affect our results could not be controlled. These variables include, but are not limited to, the quality of MRSA nasal screen collection, type of respiratory culture obtained, and timing of antibiotic administration to MRSA nasal screen or respiratory culture results. Furthermore, patients who underwent MRSA nasal decolonization and those who received at least 48 hours of anti-MRSA antibiotics in the 30 days prior to nasal screen were excluded; thus, the performance characteristics and possible utility of the MRSA nasal screen cannot be extrapolated to such patients. As mentioned previously, we did not analyze the impact of the duration of time between MRSA nasal screen and pneumonia diagnosis, as the majority of our nasal screens were obtained a median 1 day prior to pneumonia diagnosis. A comparison of clinical outcomes (eg 30-day mortality, length of hospitalization, acute kidney injury) between patients that received anti-MRSA antibiotics (77/98) to those who did not (20/98) was not feasible given the significant heterogeneity in clinical outcomes in AML and HCT patients and competing risks of underlying disease on clinical outcomes. Finally, our results may not be generalizable to units or facilities with a higher prevalence of MRSA pneumonia.

In conclusion, we found that that MRSA pneumonia is uncommon in hospitalized patients with AML with or without HCT, and the decision to start empiric anti-MRSA antibiotics should be carefully considered, especially in those with prior recent negative MRSA nasal surveillance. In addition, for hospitalized patients with AML

initiated on empiric anti-MRSA therapy, a MRSA nasal surveillance culture may aid in more rapid de-escalation.

CONFLICT OF INTEREST

The authors declared no conflict of interest related to the topic.

AUTHOR CONTRIBUTIONS

MT participated in the study design, data collection, data analysis, initial draft, and revision of the manuscript. BLM participated in the study design, data analysis, initial draft and revision of the manuscript. TSP, GBS, AJP, and AS participated in the study design, data analysis, and manuscript review. LAP, KMP, PWB, and DLB participated in the manuscript review.

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How to cite this article: Talagtag M, Patel TS, Scappaticci GB, et al. Utility of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening in patients with acute myeloid leukemia (AML). *Transpl Infect Dis*. 2021;23:e13612. https://doi.org/10.1111/tid.13612