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BRIEF REPORT

Prospective Nasal Screening for Methicillin-Resistant *Staphylococcus aureus* in Critically Ill Patients With Suspected Pneumonia

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We carried out a prospective de-escalation study based on methicillin-resistant *Staphylococcus aureus* (MRSA) nasal cultures in intensive care unit patients with suspected pneumonia. Days of anti-MRSA therapy was significantly reduced in the intervention group (2 [0–3] days vs 1 [0–2] day; $P < .01$). Time to MRSA de-escalation was also shortened in the intervention group.

Keywords. *Staphylococcus aureus*; pneumonia; screening; intensive care.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a known colonizer of the nares and other sites in hospitalized patients. Absence of nasal colonization via polymerase chain reaction (PCR) or culture-based methods has been shown to predict lack of future MRSA pulmonary infection [1–8]. In a retrospective cohort study of non–intensive care unit (ICU) patients with pneumonia or exacerbations of chronic obstructive pulmonary disease, Willis et al. compared outcomes pre- and postimplementation of a pharmacist-driven vancomycin de-escalation protocol using MRSA nasal PCR [6]. Postimplementation patients were observed to have a median reduction in vancomycin therapy of 2.1 days ($P < .0001$) and no significant differences in clinical stability, acute kidney injury, length of stay, or mortality. To date, limited data exist surrounding the clinical utility of MRSA nasal PCR/cultures in critically ill patients with pneumonia. A retrospective cohort of >11 000 ICU patients with MRSA nasal cultures estimated that 7364 vancomycin-days could have been avoided in patients who had vancomycin continued despite negative MRSA nasal cultures [3]. Smith et al. retrospectively compared critically ill patients with nosocomial pneumonia and an MRSA nasal PCR who were de-escalated with patients who continued vancomycin [7]. They observed longer ICU stay (13 vs 10 days; $P = .001$) in patients continued on vancomycin. De-escalation compliance and the prevalence of MRSA pneumonia in Willis et al. and Smith et al. were low (55.2% and 45.3% vs 4.0% and 9.3%, respectively) [6, 7]. Further, these trials focused only on vancomycin. Therefore, we sought to carry out a prospective de-escalation study based on MRSA nasal cultures in our ICU population with suspected pneumonia.

METHODS

Study Design and Patient Population

This study was conducted at the Barnes-Jewish Hospital medical ICU, a 36-bed unit within a 1300-bed academic medical center in Saint Louis, Missouri. The medical ICU has a long history of collaborative antimicrobial de-escalation based on antimicrobial culture results [9, 10]. Approval for this study was obtained from the Washington University institutional review board. Study investigators used available evidence to devise a draft de-escalation guideline. This draft was presented and discussed at various multidisciplinary meetings inclusive of physician, nursing, and pharmacy representatives to receive feedback and expert opinion, improve bedside practicality, and introduce study awareness and education. Educational initiatives in the form of in-person presentations and emails were conducted by study authors to ICU nurses, pharmacists, and physicians. Finally, weekly reminder emails to ICU staff were sent by study authors during the first month postimplementation, with subsequent reminders sent approximately monthly until study completion.

The study was designed before the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in 2019 to employ a prospective intervention group and a retrospective control group. The intervention portion was planned for January 1, 2020, to June 1, 2020. It took place during the SARS-CoV-2 pandemic and included a protocol encouraging discontinuation of anti-MRSA antibiotics for patients with suspected or proven pneumonia and negative MRSA nasal swab cultures promoted by the investigators and clinical pharmacists on daily rounds. Patients admitted to the medical ICU between January 1, 2019, and June 1, 2019, with an International Classification of Diseases, 10th Revision, Clinical Modification (ICD 10-CM) code for sepsis or pneumonia were screened retrospectively

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from a pharmacy informatics database query, and the diagnosis of pneumonia was confirmed by reviewing clinical documentation and chest radiography (N.R. and M.H.K.) for inclusion in the control group.

Patients in both the control and intervention groups had an MRSA nasal culture obtained within 24 hours of ICU admission and received an anti-MRSA antibiotic within 24 hours of ICU admission for study eligibility. Patients were excluded from the intervention group if they tested positive for SARS-CoV-2. During the intervention period, study investigators were alerted of potentially eligible patients via a real-time electronic medical record alert once all inclusion criteria were met. One of the investigators directly contacted the treating team, which included the clinical pharmacist, to recommend discontinuation of the MRSA therapy. The patient care team responsible for protocol implementation after notification from 1 of the investigators consisted of a critical care medicine board-certified attending, a critical care fellow, internal medicine residents, nursing staff, a clinical pharmacist, and a nutritionist.

The de-escalation protocol encouraged discontinuation of anti-MRSA antibiotics; however, the final decision was left to the discretion of the treating providers. Patients in both groups were excluded from the analysis if they had a positive MRSA nasal swab culture or a positive clinical culture for MRSA necessitating continuation of anti-MRSA antibiotics after finalization of the nasal swab culture. Patients were also excluded if anti-MRSA antibiotics were discontinued before finalization of the MRSA nasal swab culture. The criteria to define pneumonia were taken from the American Thoracic Society/Infectious Diseases Society of America position statement on pneumonia [11]. These diagnostic criteria included presence of a new or progressive radiographic infiltrate and ≥2 of the following clinical features: fever >38°C, leukocytosis ($>10 \times 10^9$cells/L), leukopenia ($\leq 4 \times 10^9$cells/L), or purulent respiratory secretions. The presence of a radiographic infiltrate was based on the interpretation of the chest radiograph by board-certified radiologists.

Receipt of an anti-MRSA antibiotic was defined as administration of intravenous vancomycin (or measured serum vancomycin level ≥15 mcg/mL), ceftaroline, or linezolid within the first 24 hours of ICU admission, ending at midnight. De-escalation of anti-MRSA therapy was defined as no receipt of intravenous vancomycin (or measured vancomycin level ≥15 mcg/mL), ceftaroline, or linezolid in a 24-hour period ending at midnight. Re-escalation of antibiotics was defined as re-initiation of anti-MRSA antibiotics within 7 days of discontinuation and receipt of these antibiotics on ≥2 consecutive days. In the intervention group, protocol compliance was defined as discontinuation of anti-MRSA antibiotics on the day in which nasal swab cultures resulted negative. If anti-MRSA antibiotics were not discontinued, the treating team was contacted to collect the reason for protocol noncompliance and to again recommend discontinuation. Data related to timing of antibiotic de-escalation and re-escalation and reasons for re-escalation were recorded.

We employed standard definitions for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) [9, 10]. The APACHE II score and the Charlson Co-morbidity Index were used to assess baseline severity of illness. All systemic antimicrobial administration data and culture data were also recorded. During the study period, nasal swab cultures were obtained and evaluated via Spectra MRSA chromogenic agar (Remel, Lenexa, KS, USA).

Outcomes

The primary outcome was duration of ICU anti-MRSA antibiotic therapy. Secondary outcomes included time to anti-MRSA therapy de-escalation, de-escalation protocol compliance, number of ICU days without MRSA coverage, incidence of anti-MRSA therapy re-escalation, hospital mortality, hospital length of stay, and *C. difficile* infection.

Statistical Analysis

Continuous variables were reported as means with SDs or medians with 25th and 75th percentiles according to their distribution. The Student *t* test was used for normally distributed data, and the Mann-Whitney *U* test for non–normally distributed data. Categorical data were expressed as frequency distributions, and chi-square tests were used to determine if differences existed between groups. All statistical analyses were conducted using SPSS Statistics, version 22.0 (IBM).

RESULTS

Five hundred twenty-three patients met eligibility criteria; 140 in the control group and 103 in the intervention group were included. The most common reasons for exclusion were absence of pneumonia (n = 150), discontinuation of anti-MRSA antibiotics before nasal swab culture results (n = 42), and MRSA nasal swab culture resulting as positive (n = 54).

Demographic characteristics were similar between the groups, including rates of antibiotic exposure in the preceding 90 days (Table 1). Community-onset pneumonia represented 87% of included patients. The control group had a significantly higher median lactic acid level (1.7 mg/dL vs 1.3 mg/dL; $P = .02$). The 2 groups received similar antimicrobial therapy. Most patients in each group received either linezolid or ceftaroline rather than vancomycin. Of 103 patients included in the intervention group, 47 (46%) were immediately de-escalated per protocol. Reasons for noncompliance with anti-MRSA de-escalation included recommended continuation by consultant services (N = 8; 14%), MRSA nasal swab resulting in the evening and not acted upon until after the patient had received a dose of anti-MRSA antibiotics early the following morning (N = 7; 13%), and continuation deemed warranted by the primary treatment team (N = 41; 73%).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic/Outcomes	All Patients (n = 243)	Control Group (n = 140)	Intervention Group (n = 103)	*P* Value
Age, y	60 (49–69)	61 (48–69)	58 (49–70)	.58
Male, No. (%)	128 (53)	77 (55)	51 (50)	.40
Race, No. (%)				
Caucasian	146 (60)	85 (61)	61 (59)	.82
African American	83 (34)	45 (32)	38 (37)	.44
Other	14 (6)	10 (7)	4 (4)	.28
BMI, kg/m^2	28 (23–34)	27 (23–33)	30 (23–34)	.48
Charlson comorbidity index	4 (2–6)	4 (2–7)	4 (2–6)	.20
Modified APACHE II score	14 (11–18)	14 (11–18)	14 (11–20)	.57
Pneumonia classification, No. (%)				
Community-onset	211 (87)	120 (86)	91 (88)	.55
Hospital-acquired	30 (12)	19 (14)	11 (11)	.50
Ventilator-associated	2 (1)	1 (1)	1 (1)	.83
IV antibiotic administration in last 90 d, No. (%)	80 (33)	44 (31)	36 (35)	.56
Hospitalization in last 90 d, No. (%)	88 (36)	48 (34)	40 (39)	.47
ICU admission source, No. (%)				
Outside hospital	92 (38)	55 (39)	37 (36)	.59
Emergency department	111 (46)	57 (41)	54 (52)	.07
Medical ward	40 (16)	28 (20)	12 (12)	.08
Extended care facility resident, No. (%)	24 (10)	16 (11)	8 (8)	.34
Mechanical ventilation within 24 h of ICU admission, No. (%)	133 (55)	71 (51)	62 (60)	.14
Vasopressor exposure within 24 h of ICU admission, No. (%)	106 (44)	58 (41)	48 (47)	.42
Lactate before antimicrobial initiation, mg/dL	1.6 (1–2.5)	1.7 (1.2–2.4)	1.3 (0.8–2.5)	.02
WBC before antimicrobial initiation, k/mm^3	11.0 (7.0–15.5)	11.2 (6.8–16.9)	10.9 (7.7–15.0)	.82
eCrCl nearest ICU admission, mg/dL	50 (27–76)	51 (29–75)	53 (22–78)	.81
RRT during ICU stay, No. (%)	25 (10)	10 (7)	15 (15)	.06
Time from ICU admit to MRSA nasal culture attainment, h	1 (0–1)	1 (0–1)	1 (0–1)	.67

Data are reported as median (IQR) unless otherwise noted.

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; BMI, body mass index; eCrCl, estimated creatinine clearance (using the Cockcroft-Gault formula); ICU, intensive care unit; IQR, interquartile range; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; RRT, renal replacement therapy; WBC, white blood cell count.

The primary end point of days of ICU anti-MRSA therapy was significantly reduced in the intervention group (Table 2). The time to MRSA de-escalation was shortened in the intervention group, which also had more ICU days without anti-MRSA therapy. Re-initiation of anti-MRSA therapy was infrequent in both groups (13% vs 11%; $P = .61$). Reasons for re-initiation included new or worsening pneumonia, new or worsening sepsis, and suspected central nervous system (CNS) infection;

Table 2. Clinical Outcomes

Outcomes	All Patients (n = 243)	Control Group (n = 140)	Intervention Group (n = 103)	*P* Value
Days of ICU anti-MRSA therapy	1 (0–3)	2 (0–3)	1 (0–2)	<.01
Time to anti-MRSA de-escalation, days	2 (1–3)	3 (0–3)	1 (0–2)	.01
Days of ICU admission without anti-MRSA therapy	2 (0–5)	1 (0–4)	3 (1–6)	<.01
Re-initiation of anti-MRSA therapy after de-escalation, No. (%)	29 (12)	18 (13)	11 (11)	.61
Reason for re-initiation, No. (%)				
New or worsening pneumonia	N/A	N/A	4/11 (36)	N/A
New or worsening sepsis			4/11 (36)	
New gram-positive infection			0/11 (0)	
Suspected CNS infection			2/11 (18)	
Other			1/11 (9)	
In-hospital mortality, No. (%)	40 (16)	20 (14)	20 (19)	.29
Hospital LOS, d	9 (6–18)	9 (6–15)	9 (6–19)	.37
C. diff positive during index hospitalization, No. (%)	4 (2)	3 (2)	1 (1)	.64
No. of vancomycin levels obtained	0 (0–2)	0 (0–2)	0 (0–1)	.01

Data are reported as median (IQR) unless otherwise noted.

Abbreviations: *C. diff*, *Clostridium difficile*; CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*.

no patients were restarted on MRSA antimicrobials for a proven gram-positive infection. Hospital mortality and hospital length of stay were similar for the 2 groups. *C. difficile* positivity rates were similar for the 2 groups.

DISCUSSION

In this study, de-escalation of empiric anti-MRSA antimicrobials for treatment of pneumonia in the ICU following a negative MRSA nasal swab culture resulted in a shorter duration of anti-MRSA therapy without increased in-hospital mortality, hospital duration, or rates of antibiotic re-initiation. Following de-escalation, no patients required re-escalation for a subsequent MRSA infection during their hospital stay.

To the best of our knowledge, this is the first study to prospectively evaluate an MRSA antimicrobial de-escalation protocol for pneumonia in the ICU setting. Furthermore, unlike previously published studies, most patients received either linezolid or ceftaroline, rather than vancomycin. At our institution, systematic antimicrobial stewardship protocols are already in place, and unlike the present study, prior implementation of an enhanced antimicrobial de-escalation team in the ICU did not lead to a reduction in the duration of antibiotic therapy [9].

As our study evaluated patients upon admission to the ICU, most patients had community-onset pneumonia, and only 2 patients had VAP. Given the lower incidence of MRSA as the etiology of community-onset pneumonia, the utility of empiric anti-MRSA therapy may be lower and the negative predictive value of nasal swab testing is higher. Strict compliance with the de-escalation protocol only occurred 46% of the time, though duration of MRSA therapy was significantly shortened following protocol implementation. Though the control and intervention groups were admitted to the same ICU at similar times of the year, there were baseline differences, as reflected by the significantly higher lactic acid levels in the control group. Moreover, the intervention occurred during the SARS-CoV-2 pandemic, introducing potential patient population differences that may have biased our results despite our exclusion of patients with SARS-CoV-2 infection. We also included patients with suspected pneumonia in the intervention group, who can only benefit from de-escalation of antibiotics if pneumonia is excluded. Another limitation of our study is that the ultimate decision to de-escalate antibiotics was left up to the treating physicians, which may have also influenced de-escalation practices and biased our results.

In conclusion, in an academic medical center with systematic antimicrobial stewardship protocols already in place, implementation of a protocol for MRSA antimicrobial de-escalation for ICU patients with a diagnosis of pneumonia based on nasal MRSA cultures led to a shorter duration of anti-MRSA antibiotics without an increase in in-hospital mortality, length of stay, or rates of antibiotic re-initiation. Our study demonstrates that MRSA screening can reduce unnecessary use of anti-MRSA antibiotics in an MRSA-low-risk population. However, these results may not apply to patients with hospital-acquired or ventilator-associated pneumonia, for whom the likelihood of MRSA infection would be greater.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This study does not include factors necessitating patient consent and the need for informed consent was waived by the Washington University Institutional Review board.

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