CHEST

Outcomes Associated With De-escalating Therapy for Methicillin-Resistant *Staphylococcus aureus* in Culture-Negative Nosocomial Pneumonia

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BACKGROUND: In culture-positive nosocomial pneumonia, de-escalation (DE) from broad-spectrum empirical antimicrobials to narrower-spectrum agents has shown to decrease broad-spectrum antibiotic use without compromising patient outcomes. However, uncertainty exists regarding the safety of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agent DE in culture-negative nosocomial pneumonia. This study aimed to determine if anti-MRSA agent DE in culture-negative nosocomial pneumonia affects 28-day and hospital mortality, ICU and hospital length of stay (LOS), treatment failure, and safety.

METHODS: This single-center retrospective cohort study included adult patients admitted from 2012 to 2017 with nosocomial pneumonia and a negative respiratory culture. DE was defined as anti-MRSA agent discontinuation within 4 days of initiation. Secondary outcomes included hospital mortality, hospital and ICU LOS, treatment failure, and occurrence of acute kidney injury (AKI).

RESULTS: Of 279 patients included, 92 were in the DE group and 187 were in the no DE (NDE) group. Patients who were not de-escalated received 5 more days of MRSA coverage than patients who were de-escalated; however, there was no difference in 28-day mortality (NDE group, 28% vs DE group, 23%; difference, −5.5%; 95% CI, −16.1 to 6.5). Patients who were de-escalated had shorter hospital (DE group, 15 days vs NDE group, 20 days; difference, 3.2 days; 95% CI, 0.1-6.4) and ICU (DE group, 10 days vs NDE group, 13 days; difference, 2.2 days; 95% CI, −0.3 to 4.9) LOSs after the index date. The incidence of AKI was significantly higher in patients who were not de-escalated (DE group, 36% vs NDE group, 50%; difference, −13.8%; 95% CI, −26.9 to −0.4).

CONCLUSIONS: Although anti-MRSA agent DE in culture-negative nosocomial pneumonia did not affect 28-day mortality, it was associated with a shorter hospital LOS and lower incidence of AKI.

CHEST 2019; 155(1):53-59

KEY WORDS: de-escalation; methicillin-resistant *Staphylococcus aureus*; pneumonia

ABBREVIATIONS: AKI = acute kidney injury; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: https://doi.org/10.1016/j.chest.2018.10.014

Nosocomial pneumonia, which accounts for 22% of hospital-acquired infections, has a mortality rate of 20% to 50% in patients who are critically ill.[1,2] These infections are commonly caused by multidrug-resistant organisms such as *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA).[3] *S aureus* has been independently associated as a risk factor for death, with a mortality rate of up to 50%.[4,5] However, MRSA as the cause of nosocomial pneumonia is declining.[6] Because of the morbidity associated with inadequate coverage, guidelines recommend broad-spectrum empirical therapy including MRSA coverage.[2,3]

Although empirically covering patients with broad-spectrum antibiotics for nosocomial pneumonia is appropriate, the use of anti-MRSA antibiotics, such as vancomycin and linezolid, can result in the development of adverse drug events and antibiotic resistance.[7] Vancomycin has been associated with nephrotoxicity in numerous studies, with rates noted from 5% to 43%.[8,9] In some analyses, risk factors for vancomycin-associated nephrotoxicity include doses > 4 g daily, supratherapeutic troughs > 20 mg/dL, critical illness, and durations of therapy > 7 days.[8] Linezolid has been associated with serotonin syndrome and hematologic effects such as neutropenia and thrombocytopenia. Neutropenia and thrombocytopenia, which have been reported to occur in around 3% to 5% of patients, usually occur with use > 14 days and is reversible on discontinuation.[10] Another risk of antimicrobial use is progressive loss of antibiotic activity with the potential development of resistance. There has been evidence of increasing vancomycin minimum inhibitory concentrations with MRSA over time.[11] Furthermore, in some analyses, vancomycin minimum inhibitory concentrations > 1.5 μg/mL have been associated with an increased risk of treatment failure.[12]

De-escalation of antimicrobials has been proposed as a method for transitioning broad-spectrum antimicrobial usage to narrower-spectrum agents to curtail the adverse consequences associated with prolonged antimicrobial therapy. De-escalation of unnecessary antimicrobials most commonly occurs with the presence of positive culture results and the ability to target the inciting pathogen. However, for many patients with nosocomial pneumonia, cultures remain negative, making de-escalation to a targetable pathogen difficult. This study aimed to determine if de-escalation of anti-MRSA agents in culture-negative nosocomial pneumonia affects 28-day or hospital mortality, hospital and ICU length of stay, incidence of treatment failure, or incidence of acute kidney injury (AKI).

Methods

Study Design and Patient Population

This study was conducted at Barnes-Jewish Hospital, a 1,300-bed academic medical center in Saint Louis, Missouri. Approval for this study was obtained from the Washington University institutional review board, and the need for informed consent was waived given the retrospective cohort study design. All methods and definitions were decided on prior to data collection. All adult patients with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) or *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code for pneumonia between January 2012 and December 2016 were eligible for inclusion. Patients were subsequently screened to identify those with nosocomial pneumonia, defined as an index date of infection that was > 48 h after hospital admission, findings consistent with pneumonia on chest radiography, and at least one sign of infection, including leukocytosis > 10×10^9 cells/L, leukopenia ≤ 4×10^9 cells/L, or fever ≥ 38.0° C. All chest radiographs were reviewed by one of the investigators (M. H. K.) to confirm the presence of a new or progressive infiltrate consistent with pneumonia. In addition, patients had to have a respiratory culture drawn and an anti-MRSA agent started on the index date. Patients were excluded if a pathogen was identified from a respiratory specimen 7 days prior to through 4 days after the index date. Respiratory cultures that were reviewed included BAL cultures, sputum cultures, and tracheal aspirates. Negative respiratory specimens were defined as cultures with no growth, normal respiratory flora, or a nonpathogenic colonizer (eg, *Candida* and *Enterococcus* species). Anti-MRSA agents included in the study were vancomycin, linezolid, and ceftaroline. Additionally, patients were excluded if they had a diagnosis of cystic fibrosis, had received a lung transplant, or were admitted to any oncology or hematologic malignancy ward. Patients with cystic fibrosis and patients who had received a lung transplant were excluded because of the significance of all previous cultures and the propensity to treat previous pathogens even if not isolated during the current infection. Patients on the oncology or hematologic malignancy wards were excluded because of the possibility of neutropenic fever, in which case guideline recommendations would dictate to continue the anti-MRSA agent in the absence of a targetable pathogen. Patients were also excluded because of a lack of an index date, if the index date did not occur > 48 h after admission, or if the patient did not have signs of infection, did not have a respiratory culture taken, or did not have an anti-MRSA agent started on the index date.

Patients were classified as having ventilator-associated pneumonia (VAP) if they had been mechanically ventilated for ≥ 48 h prior to pneumonia diagnosis. The Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, modified to exclude the Glasgow Coma Scale score, was used to assess baseline severity of illness. To determine if severity of illness changed during therapy, the incidence of ICU transfer, mechanical ventilation, and addition of a vasopressor were also assessed from index date to day 4. De-escalation of other antimicrobials was assessed only when patients had active orders for the other agent(s) on the index date and was defined as the discontinuation of the antimicrobial by day 4.

Outcomes

Patients were divided into two groups based on whether the anti-MRSA agent started on the index date was discontinued within

4 days (de-escalation group) or continued (no de-escalation group). Discontinuation within 4 days allowed 3 days for cultures to return and 1 day for medical teams to react to culture results.

The primary outcome was 28-day mortality after index date. The 28-day mortality was confirmed through subsequent health-system records and the Social Security Death Index. Secondary outcomes included treatment failure defined as restarting the MRSA agent between 2 and 7 days after discontinuation, hospital mortality, total length of ICU and hospital stay, length of ICU and hospital stay after index date, and development of AKI. AKI was assessed in all patients except patients with an ICD-9-CM or ICD-10-CM code for end-stage renal disease. Stage 1 AKI was defined, per the Kidney Disease: Improving Global Outcomes Guidelines,[13] as an increase in serum creatinine of $\geq$ 0.3 or an increase of $\geq$ 1.5 times the baseline serum creatinine, which was determined on the index date. Stage 2 and stage 3 AKI were further defined as an increase of 2.0 to 2.9 or $\geq$ 3 times the baseline serum creatinine, respectively.

From January 2002 through the present, Barnes-Jewish Hospital used an antibiotic control program to help guide antimicrobial therapy for bacterial infections. During this time, the use of azithromycin, ceftriaxone, cefepime, gentamicin, and vancomycin was unrestricted. However, initiation of IV ciprofloxacin, imipenem, meropenem, piperacillin/tazobactam, ceftolozane/tazobactam, ceftazidime/avibactam, linezolid, or ceftaroline was restricted and required preauthorization from either a clinical pharmacist or infectious diseases physician. Each ICU and hospital ward had a clinical pharmacist who reviewed all antibiotic orders to ensure that dosing and interval of antibiotic administration was adequate for individual patients based on body size, renal function, and the resuscitation status of the patient.

Statistical Analysis

Continuous variables were reported as means with SDs or medians with 25th and 75th percentiles according to their distribution. Student *t* test was used when comparing normally distributed data, and Hodges-Lehmann estimate was used to analyze nonnormally distributed data. Categorical data were expressed as frequency distributions, and χ^2 or Fisher exact test was used to determine if differences existed between groups. Results from these analyses are presented as point estimates with their 95% CIs. The relationship between time to 28-day mortality and de-escalation and no de-escalation was evaluated by the Kaplan-Meier method using the log-rank test. All statistical analyses were conducted using SPSS Statistics version 22.0 (IBM).

Results

Patient Characteristics

Of 1,898 patients with an ICD-9-CM or ICD-10-CM code for pneumonia, 279 patients were included, with 92 patients who had their anti-MRSA agent de-escalated by day 4, and 187 patients in whom de-escalation did not occur. Of the 1,898 patients, 1,177 patients were excluded because of a lack of an index date, 428 were excluded for having a positive respiratory culture, seven patients died within 4 days, and seven patients had received a lung transplant. Most patients were white men, and many patients had a high level of critical illness as indicated by admission to an ICU (87%) and a median modified APACHE II score of 13 at the time of pneumonia diagnosis. VAP was diagnosed in 56% of patients, and 44% had a non-VAP nosocomial pneumonia diagnosis. Although no patients had positive respiratory cultures, 13% of patients had positive cultures at other sites, consistent with concomitant infections. The most common concomitant infection was bloodstream infection. Nosocomial pneumonia was diagnosed at a median of hospital day 7. Most patients were treated with an antipseudomonal agent (92%), and vancomycin was the most common empirical anti-MRSA agent chosen (78%).

Baseline characteristics were similar between groups (Table 1); however, a significantly higher number of patients had chronic kidney disease in the de-escalation group (43% vs 32%, respectively). There was no difference in the change of severity of illness from index date to day 4, as seen by the incidence of patients transferred to the ICU, intubated, and started on a vasopressor. Of the patients who were not already in the ICU, mechanically ventilated, and on a vasopressor at baseline, 11 of 24 patients (46%) vs seven of 12 patients (58%) were transferred to the ICU, 31 of 74 patients (42%) vs 14 of 36 patients (39%) were intubated, and 57 of 112 patients (51%) vs 25 of 58 patients (43%) required the addition of a vasopressor in the no de-escalation group and the de-escalation group, respectively. Notably, patients who had their anti-MRSA agents de-escalated by day 4 were more likely to have their antipseudomonal agent de-escalated (61/84; 73% vs 38/174; 22%, respectively) vs patients whose anti-MRSA agent was not de-escalated.

Outcomes

Overall, patients who were in the de-escalation group had 5 fewer days of anti-MRSA therapy than patients who were not de-escalated (Table 2). The primary end point of 28-day mortality was not different between the groups (de-escalation: 23% vs no de-escalation: 28%; difference, −5.5; 95% CI, −16.1 to 6.5). A Kaplan-Meier survival curve showed no difference in time to event between groups (log-rank $P = .389$) (Fig 1). There was a difference in ICU and hospital length of stay after index date, with patients who were de-escalated being transferred out of the ICU 3 days earlier and discharged from the hospital 5 days earlier. There was no difference in treatment failure between the groups (Table 2).

Incidence of AKI

In an evaluation of the incidence of AKI between groups, patients who had their anti-MRSA agent de-escalated had a lower incidence of AKI than patients

TABLE 1] Baseline Characteristics

Characteristic	De-escalation Group (n = 92)	No De-escalation Group (n = 187)	Difference (95% CI)
Male	63 (68.5)	107 (57.2)	11.3 (−1.8 to 23.2)
Age, y	60.7 (47.5-71.2)	61.8 (49.0-72.2)	−0.6 (−3.7 to 4.9)
Race			
White	69 (75.0)	132 (70.6)	4.4 (−7.8 to 15.3)
Black	21 (22.8)	42 (22.5)	0.4 (−10.1 to 12.0)
Other	2 (2.2)	13 (7.0)	−4.8 (−7.4 to 1.9)
Comorbidities			
COPD	48 (52.2)	91 (48.7)	3.5 (−9.7 to 16.6)
Diabetes	35 (38.0)	59 (31.6)	6.4 (−5.9 to 19.3)
Heart failure	35 (38.0)	87 (46.5)	−8.5 (−21.0 to 4.7)
Chronic renal failure	40 (44.6)	59 (32.1)	12.5 (−0.003 to 25.3)
End-stage renal disease	12 (13.0)	17 (9.1)	4.0 (−3.9 to 12.6)
Hepatic cirrhosis	24 (26.1)	44 (23.5)	2.6 (−8.4 to 14.4)
Solid organ transplant	4 (4.3)	7 (3.7)	0.6 (−3.7 to 6.2)
Charlson Comorbidity Index score	6 (4-8)	6 (3-8)	0.0 (−1.0 to 0.0)
Modified APACHE II score	13 (10-18)	13 (9-17)	−0.0 (−2.0 to 1.0)
Type of nosocomial pneumonia			
Non-VAP	41 (44.6)	82 (43.9)	0.7 (−12.2 to 13.9)
VAP	51 (55.4)	105 (56.1)	−0.7 (−13.9 to 12.2)
ICU admission at baseline	80 (87.0)	163 (87.2)	−0.2 (−9.8 to 7.8)
Active order for a vasopressor at baseline	34 (37.0)	75 (40.1)	−3.2 (−9.9 to 15.6)
Concomitant infection			
Bacteremia	7 (7.6)	11 (5.9)	1.7 (−4.2 to 8.8)
Clostridium difficile infection	5 (5.4)	4 (2.1)	3.3 (−1.5 to 7.5)
Other	6 (6.5)	6 (3.2)	3.3 (−2.0 to 8.6)
Concomitant antimicrobial use at baseline			
Antipseudomonal antibiotic	84 (91.3)	174 (93.0)	−1.7 (−9.4 to 4.7)
Antibiotic without pseudomonal activity	26 (28.3)	36 (19.3)	9.0 (−2.1 to 20.5)
Antifungal	11 (12.0)	27 (14.4)	−2.6 (−10.2 to 7.3)
Day of hospitalization diagnosed with pneumonia	7.4 (3-16)	7.2 (3-16)	0.0 (−1.5 to 1.5)
Anti-MRSA agent used			
Vancomycin	76 (82.6)	143 (76.5)	6.1 (−5.2 to 15.5)
Linezolid	15 (16.3)	43 (23.0)	−6.7 (−15.8 to 4.5)
Ceftaroline	1 (1.1)	1 (0.53)	0.6 (−1.0 to 2.1)

Results are listed as median (interquartile range) for continuous variables, No. (%) for other variables, or as otherwise indicated. APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

who had their anti-MRSA agent continued (29/80; 36% vs 85/170; 50%; difference, −13.8%; 95% CI, −26.9 to −0.4). In the no de-escalation group, 62 patients experienced a stage 1 AKI, 14 patients experienced a stage 2 AKI, and nine patients had their serum creatinine increase by > 3 times the baseline during treatment. In the de-escalation group only 27 patients experienced a stage 1 AKI, two patients experienced a stage 2 AKI, and no patients had a stage 3 AKI.

Discussion

In this retrospective cohort study, de-escalation of an empirical anti-MRSA agent in culture-negative nosocomial pneumonia did not affect 28-day mortality.

TABLE 2] Patient Outcomes

Outcome	De-escalation Group (n = 92)	No De-escalation Group (n = 187)	Difference (95% CI)
Duration of treatment	3.0 (2-4)	8.0 (7-11)	5.0 (5.0 to 6.0)
Primary outcome			
28-d mortality	21 (22.8)	53 (28.3)	−5.5 (−16.1 to 6.5)
Secondary outcomes			
Hospital mortality	27 (29.3)	56 (30.0)	−0.6 (−12.1 to 11.9)
Treatment failure	23 (25.0)	32 (17.1)	7.9 (−2.7 to 19.0)
Total hospital length of stay, d	27 (18-46)	30 (18-47)	3.0 (−2.0 to 8.0)
Hospital length of stay after index date, d	15 (8-30)	20 (11-34)	3.2 (0.1 to 6.4)
Total ICU length of stay, d	21 (11-38)	22 (13-35)	1.2 (−2.9 to 5.2)
ICU length of stay after index date, d	10 (5-24)	13 (8-23)	2.2 (−0.3 to 4.9)

Results are listed as median (interquartile range) for continuous variables, No. (%) for other variables, or as otherwise indicated.

Anti-MRSA agent de-escalation was also not associated with worse outcomes, such as hospital mortality, total hospital and ICU length of stay, and treatment failure. Furthermore, this study also found that patients who had their empirical anti-MRSA agent de-escalated had shorter hospital length of stay by 5 days. The shorter hospital length of stay is unlikely to be an indication of severity of illness because patient populations were well matched at baseline. Instead, the shorter length of stay may be a marker of either patients staying in the hospital extra days to receive IV antibiotics, or could be because of increased lengths of stay associated with the increased rate of AKI.[14] Because most AKIs were stage 1, it is more likely that the shorter hospital length of stay was related to the extended duration of IV antibiotic administration.

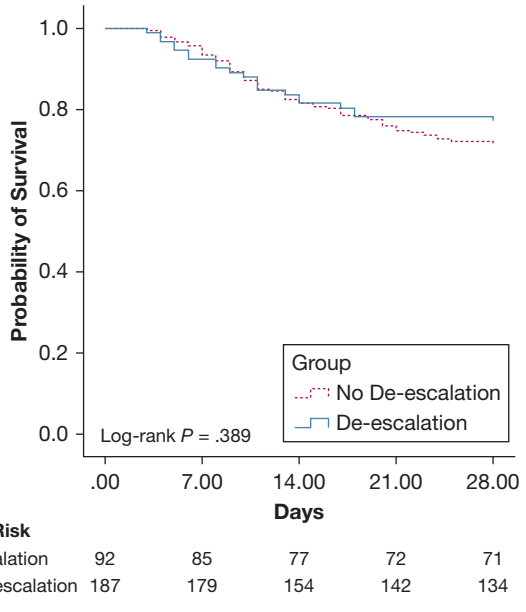

Figure 1 – *Kaplan-Meier curve for 28-d survival.*

These results are supported by several de-escalation studies conducted in patients with VAP.[15-18] In a prospective patient follow-up study, Kollef and Kollef[18] assessed patients with VAP and a culture-negative BAL to determine if de-escalation on improvement of signs and symptoms of pneumonia affected mortality. They found no difference in mortality, and although the decision to de-escalate was based on clinical signs, they proposed de-escalation may be acceptable in patients with a negative BAL. These results were also confirmed by a retrospective study by Raman et al,[7] which assessed mortality in patients with VAP who were de-escalated based on a negative BAL. De-escalation was defined by any change in antibiotics resulting in a narrower spectrum agent being used. They also found no difference in mortality.[7] Notably, however, both of these studies used negative BAL results as the basis for de-escalation. Guidelines do not recommend obtaining invasive quantitative culture in all patients, instead recommending noninvasive semi-quantitative cultures to diagnose pneumonia.[2] Comparatively, our study included any respiratory culture to make the patient population more concordant with guideline recommendations and clinical practice.

De-escalating antimicrobials has been shown in the literature to decrease drug-related adverse effects and antimicrobial expenditures.[19] In our study, a secondary outcome of safety focused on the incidence of AKI in the two groups. Patients who were not de-escalated had higher rates of AKI. Many factors that can contribute to AKI in the critically ill population were not taken into account in this secondary outcome analysis. However,

one explanation for this result is potentially associated with vancomycin use, which was the most used anti-MRSA agent in this study. Previous studies have cited prolonged duration of vancomycin as a risk factor for nephrotoxicity. In this study, patients who were de-escalated had 5 days fewer of anti-MRSA coverage than patients who were continued on their anti-MRSA agent. Additionally, of patients who received vancomycin, patients in the no de-escalation group had 2.19 more troughs drawn per patient. Although no formal economic analysis was conducted for this study, cost savings could potentially be tied to the decreased antimicrobial use, shorter lengths of ICU and hospital stay, and less adverse drug effect management.

A major limitation of this study is the retrospective design, which could have introduced bias in the selection of the cohorts. Another limitation of our study is that it may have been underpowered to identify differences in outcome parameters, such as length of stay. Because this study was retrospective in nature and may have been underpowered, there is concern for one patient population appearing more critically ill to the providers at the time of treatment because of factors that were unaccounted for in the baseline characteristics of this study. For example, patients who had their anti-MRSA agent de-escalated within 4 days had higher rates of antipseudomonal de-escalation, which could indicate there was less concern for nosocomial pneumonia in those patients. However, the baseline characteristics between the patient populations did not indicate one group was more critically ill than the other, and the events that occurred during the de-escalation study period, such as ICU transfer, intubation, and addition of a vasopressor, were also not different between groups. Another limitation of this study is the specific patient population that was chosen. All patients that were included had a respiratory culture taken on the same day an anti-MRSA agent was started, limiting the generalizability to patients receiving an anti-MRSA agent before pneumonia diagnosis, or in patients in whom a respiratory culture was never obtained. Although this study conducted an analysis of kidney dysfunction, other organ function markers of either severity of illness or adverse events related to de-escalation were not analyzed. Another limitation is the lack of data regarding incidence of *Clostridium difficile* infections after treatment. Finally, with the large population of patients who received vancomycin as their anti-MRSA agent in this study, the rates and severity of AKI may be overstated for a patient that receives linezolid for empirical MRSA coverage in nosocomial pneumonia.

In conclusion, de-escalation of an empirical anti-MRSA agent in culture-negative nosocomial pneumonia did not affect 28-day mortality and may have led to a lower rate of AKI. Further studies could further delineate the association between de-escalation and AKI for vancomycin and linezolid.

Acknowledgments

Author contributions: M. C. C. and S. T. M. are the guarantors of and take responsibility for the content of the manuscript, including the data and analysis. All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; drafted the submitted article or revised it critically for important intellectual content; provided final approval of the version to be published; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: M. H. K.'s effort was supported by the Barnes-Jewish Hospital Foundation. None declared (M. C. C., D. J. R., N. H., S. T. M.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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