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BRIEF REPORT

Outcomes Associated With Antimicrobial De-escalation of Treatment for Pneumonia Within the Veterans Healthcare Administration

Jefferson G. Bohan,[1] Richard Remington,[2,3] Makoto Jones,[4] Matthew Samore,[4] and Karl Madaras-Kelly[1,5]

Departments of [1]Pharmacy and [2]Research, Boise Veterans Affairs Medical Center, Boise, Idaho; [3]Quantified Inc., Boise, Idaho; [4]Department of Medicine, George E. Wahlen Veterans Affairs Medical Center and Division of Epidemiology, University of Utah, Salt Lake City, Utah; [5]College of Pharmacy, Idaho State University, Meridian, Idaho

De-escalation, an antimicrobial stewardship concept, involves narrowing broad-spectrum empiric antimicrobial therapy based on clinical data. Current health outcomes evidence is lacking to support de-escalation. Studying Veterans Healthcare Administration pneumonia patients, de-escalation was associated with improved length of stay without affecting 30-day readmission or 30-day *Clostridium difficile* infection rates.

Keywords. antimicrobial stewardship; de-escalation; outcomes; pneumonia.

The Infectious Diseases Society of America, Centers for Disease Control and Prevention, and White House's National Action Plan for Combating Antibiotic-Resistant Bacteria recommend developing, implementing, and maintaining antimicrobial stewardship programs (ASP) in acute care settings [1–3]. De-escalation, an ASP concept, involves narrowing the spectrum of empiric antimicrobial therapy based on diagnostic data and clinical improvement, usually 2–3 days after empirical antibiotic initiation. Facilitation of de-escalation occurs through several resource-intensive activities including prospective audit and feedback, intravenous to oral switch, and antibiotic time-outs [1]. A SHEA research network survey of 61 inpatient ASPs reported a median of 9 interventions per 100 hospital beds per week, suggesting that only a fraction of eligible patients on antimicrobial therapy receive audit and feedback, including de-escalation, due to high workload burden [4].

Although systematic evaluation of de-escalation opportunities is recommended and generally results in decreased overall antimicrobial use, most evidence describing outcomes associated with de-escalation are reported from retrospective single-center studies of poor design [5, 6]. A systematic review only identified 2 open-label randomized studies and 12 small cohort studies that evaluated clinical outcomes associated with de-escalation [7]. Significant heterogeneity was identified, <50% of the studies used multivariable analysis, and only 2 studies used propensity score analyses adjusting for confounders associated with the intervention and outcome.

To improve evaluation of de-escalation, we developed a method to better identify whether de-escalation was performed in patients diagnosed with healthcare-associated pneumonia (HCAP) [8–10]. The method (eg, Spectrum Score method), which can be applied to electronic medical records data without requiring manual chart review, is based on a numerical score that quantifies relative antibacterial activity of antimicrobials. It has demonstrated dependable concurrence with expert judgements in predicting de-escalation events in case-based vignettes [8, 9]. The method has previously been applied to evaluate de-escalation in a cohort of HCAP patients admitted to 119 Veterans Affairs (VA) facilities from 2008 to 2012 [10]. In this study, we report select clinical outcomes associated with de-escalation in that cohort.

METHODS

The retrospective cohort characteristics have been described previously [10]. Patients admitted with HCAP to acute care wards of VA facilities containing at least 10 acute care beds and 15 pneumonia admissions were identified. Only patients who were admitted for 5–14 days and received systemic antibiotics for ≥3 days were included. Data collected included the following: demographics, antimicrobial administration data, residential location before and after admission, admitting and discharge wards, past medical history, prior antibiotic exposures, laboratory values, vital signs, and microbial cultures. Outcomes data included 30-day readmission, length of stay (LOS), and 30-day *Clostridium difficile* infection (CDI) identified by laboratory identification (Lab ID) [11].

The Spectrum Score method assigns a numerical score (0–60) calculated daily based on antimicrobial agent or combination regimen administered while accounting for spectrum of activity and route of administration. Higher spectrum scores indicate broader spectrum of activity; lower scores indicate narrower spectrum of activity. For example, a broad-spectrum regimen consisting piperacillin/tazobactam and vancomycin yields a score of 44.5. De-escalation is determined by subtracting

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Correspondence: K. Madaras-Kelly, PharmD, MPH, 500 W Fort St, Bldg T-111, Boise, ID 83702 (karl.madaras-kelly2@va.gov)

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calendar day 4 spectrum scores from baseline scores computed on calendar day 2 of hospitalization. Positive change indicates de-escalation; negative change indicates escalation [8–10].

Propensity score matching was used to adjust baseline patient and treatment differences potentially confounded with de-escalation and clinical outcomes. Logistic regression models were developed to estimate the probability of receiving antimicrobial de-escalation from cohort patient data. All covariates that represented events occurring before day 4 of hospitalization (day on which de-escalation was assessed) that were associated ($P = .05$) with either de-escalation or clinical outcomes of interest were included. Baseline and clinical covariates considered included those occurring before admission, on the day of admission, and admission through hospital day 3 (Supplementary Data1). The probability to have therapy de-escalated by day 4 of hospitalization was then estimated for the whole cohort; patients who had therapy de-escalated were matched (1:1) with patients who did not have therapy changed based on a maximal caliper width of 0.2 standard deviations (SDs) of the logit of propensity scores [12]. Patients were excluded from analysis if important clinical covariate data for each outcome were missing or did not match in the propensity analyses. Patients were excluded from the 30-day CDI analysis if they had a positive CDI Lab ID within 14 days before the index admission date.

To test for associations between clinical outcomes and de-escalation, a linear regression model for LOS and logistic regression models for 30-day CDI and 30-day readmission were developed. Variables were classified based on potential for association with each outcome (low, moderate, or high potential). Outcome models were constructed by backwards selection of variables with the highest potential for association. Subsequently, variables of moderate and low potential for association were added to the models one at a time to improve model fit and assess confounding. Plausible interactions were then assessed. Akaike's Information Criterion was used to determine best fit models. To assess the impact of de-escalation on clinical outcomes, an indicator variable for de-escalation was added to each model. Odds ratios (ORs), 95% confidence intervals (CIs), and P values ($P < .05$) were calculated and reported. Analyses were conducted using statistical software R (version 3.1.2). The research conducted complies with all federal guidelines and VA policies relative to Human Subjects and Research.

RESULTS

The retrospective cohort included 9319 patients diagnosed with HCAP. Cohort demographics include mean (SD) age of 72.5 (SD = 12.1) years, 97.8% males, 11.6% intensive care unit (ICU) admission rate, 21.7% culture positive rate, and 28.3% de-escalation rate [10]. Crude 30-day readmission, 30-day CDI, and mean (SD) LOS endpoints were 29.2%, 1.6%, and 7.6 (SD = 2.6) days, respectively. The numbers (percentage of de-escalated cohort) of propensity matched pairs for 30-day readmission, 30-day CDI, and LOS endpoints were 1566 (59.7%), 1642 (59.4%), and 1575 (62.2%), respectively. Across the 3 outcome analyses, 36%–39% of cases were excluded due to missing data. Of de-escalated patients (n = 2637) only 0, 5, and 9 patients were not matched for LOS, readmission, and CDI outcomes, respectively. Table 1 presents demographics, baseline characteristics, and common baseline antibiotic characteristics of the total unmatched and propensity-matched cohorts for each outcome.

De-escalation was neither associated with 30-day readmission (OR, 0.79; 95% CI, 0.55–1.14) nor 30-day CDI (OR, 1.44; 95% CI, 0.79–2.63). De-escalation was associated with decreased LOS (mean difference, −0.28 days; 95% CI, −0.45 to −0.12). Supplementary Data2 illustrates full regression models for each clinical outcome.

DISCUSSION

To our knowledge, here we report the first study of patient outcomes related to de-escalation in a nationwide healthcare system. Thirty-day readmission and 30-day CDI were not affected by de-escalation by day 4 of hospitalization. De-escalation was associated with a modest reduction in LOS, even though all patients were hospitalized for at least 5 days, which was a day after de-escalation measurement. These data suggest that de-escalation of broad-spectrum antibiotics is safe in HCAP patients, and on average for every 4 patients de-escalated, overall LOS would be decreased by 1 day.

Strengths include data from a large, nationwide multicentered cohort of patients within the VA healthcare system, the impartial method for measurement of de-escalation, and use of multivariable analyses methods and propensity matching to adjust for confounders associated with the intervention and outcomes. This cohort, which was developed specifically to study de-escalation, provided robust clinical data and sufficient cases with clinical endpoints to conduct multivariable analyses. Use of the spectrum score method provided an objective definition that was used to identify de-escalation events. Lastly, we controlled for potentially confounding variables, which is in contrast to many prior investigations of de-escalation on clinical outcomes [13, 14].

Limitations include the retrospective design, a sizeable patient exclusion rate for the outcomes analyses based on a 5-day minimum stay required for patient inclusion, and those inherent of retrospective VA health system data [15]. In the original cohort of 31 000 HCAP cases, approximately 20 000 were excluded from the de-escalation analysis due to stays of <5 or >14 days to capture a time frame that allowed for culture results and clinical stability to be assessed [8–10]. It is possible that some patients were de-escalated and discharged before hospitalization day 5. Conversely, patients were closely matched for baseline and treatment response characteristics before de-escalation measurement, which

Table 1. Characteristics of Matched and Unmatched Outcomes Cohorts Stratified by De-escalation

	Total Cohort, Unmatched (N = 9319)		30-Day Readmits, Matched (N = 3132)		30-Day CDI, Matched (N = 3284)		LOS, Matched (N = 3150)	
Characteristic	De-esc	Not De-esc	De-esc	Not De-esc	De-esc	Not De-esc	De-esc	Not De-esc
Age (yrs), mean (SD)	72.5 (12.1)	72.5 (12.0)	73.0 (11.9)	73.1 (11.8)	72.9 (12.0)	72.9 (12.1)	73.0 (12.0)	72.8 (12.0)
Male (%)	97.4	97.9	97.4	97.8	97.5	98.0	97.5	98.3
Prior healthcare exposures (%)								
Hospital admission[a]	85.3	85.0	86.0	85.8	86.2	86.9	86.0	85.8
Skilled nursing facility residence upon admission	15.6	17.1	15.3	17.8	15.0	15.3	15.3	15.0
IV antimicrobials[b]	16.1	15.7	14.8	13.7	15.2	13.8	14.9	14.8
Wound care[b]	4.5	4.3	4.7	3.6	4.6	3.7	4.6	3.7
Chronic hemodialysis[b]	0.7	0.5	1.0	0.6	1.0	0.7	1.0	0.6
ICU admission (%)	14.1[c]	10.6[c]	5.6	5.4	8.0	7.6	5.5	4.6
Admission respiratory tract culture obtained (%)	39.3[c]	33.8[c]	37.2	36.4	37.6	38.9	37.3	36.9
Admission blood cultures obtained (%)	84.0[c]	81.3[c]	83.9	84.0	84.3	84.0	84.0	83.6
Culture-positive admission (%)[d]	28.8[c]	18.9[c]	25.7	25.5	26.1	25.6	25.8	24.9
Respiratory tract	17.7[c]	12.6[c]	16.0	15.6	16.1	16.7	16.2	15.6
Bloodstream	13.6[c]	7.6[c]	11.7	11.9	11.8	11.4	11.7	10.9
Baseline antibiotic characteristics (%)								
Median (IQR) baseline spectrum score	45.5 (42.3, 53.0)	44.0 (36.3, 45.5)	45.3 (42.0, 52.8)	44.5 (40.8, 52.8)	45.3 (42.0, 52.8)	44.5 (40.8, 52.8)	45.0 (42.0, 52.8)	44.5 (41.5, 52.8)
Double antipseudomonal + anti-MRSA coverage	21.9[c]	11.9[c]	19.5	21.1	20.2	21.3	20.2	21.3
Any antipseudomonal coverage	83.1[c]	70.0[c]	83.6[c]	80.9[c]	81.5	82.5	81.5	82.5
Any anti-MRSA coverage	65.8[c]	54.3[c]	61.7	64.6	62.8	63.7	62.8	63.7

Abbreviations: CDI, *Clostridium difficile* infection; De-esc, de-escalated; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.

[a]Within 90 days before admission.

[b]Within 30 days before admission.

[c]Indicates $P < .05$ when comparing de-escalated versus non-de-escalated groups for the total cohort and for each outcome.

[d]Culture must have been collected <12 hours before and/or ≤48 hours after admission.

reduced bias due to confounded attributes in the modeled outcomes. Although propensity score matching yielded similar groups, there will always be some degree of unmeasured confounding and bias with this approach. Unfortunately, mortality data were neither collected for the cohort nor included in the outcomes analyses. Finally, despite the relatively large cohort, 30-day CDI rates were low, which limited the precision in the estimate of association between de-escalation and 30-day CDI.

Tabah et al [7] performed a systematic review studying de-escalation and patient outcomes in 2 randomized controlled trials and 12 cohort studies in ICU patients with pneumonia. De-escalation was associated with decreased mortality, which is also supported by another recent study [5]. Opposing our study, they found no association between LOS and de-escalation. Explanations for this include the following: (1) most studies looked at ICU LOS with few studies looking at total hospital stay, and (2) comparatively, our analysis included a larger cohort of patients potentially providing increased power to detect a difference. Future work should be adequately powered and designed prospectively to determine causation between de-escalation and patient outcomes.

The impact of de-escalation on microbial resistance rates is an important endpoint that has not been elucidated. Well designed prospective studies should evaluate all important outcomes to determine whether endpoints are favorably affected. Determining the causative nature of de-escalation in addition to validation the Spectrum Score method for defining de-escalation in the non-VA setting would be beneficial.

CONCLUSIONS

In conclusion, our findings suggest de-escalation of broad-spectrum antibiotics in patients with pneumonia is safe with respect to 30-day readmission and CDI rates while modestly decreasing patient LOS.

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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