2021

Assessment of antibiotic de-escalation by spectrum score in patients with nosocomial pneumonia: A single-center, retrospective cohort study

Dan Ilges

David J. Ritchie

Tamara Krekel

Elizabeth A. Neuner

Nicholas Hampton

See next page for additional authors

Authors

Dan Ilges, David J. Ritchie, Tamara Krekel, Elizabeth A. Neuner, Nicholas Hampton, Marin H. Kollef, and Scott Micek

Open Forum Infectious Diseases

MAJOR ARTICLE

Assessment of Antibiotic De-escalation by Spectrum Score in Patients With Nosocomial Pneumonia: A Single-Center, Retrospective Cohort Study

Dan Ilges,[1] David J. Ritchie,[1,2] Tamara Krekel,[1] Elizabeth A. Neuner,[1] Nicholas Hampton,[3] Marin H. Kollef,[4] and Scott Micek[1,2]

[1]Department of Pharmacy, Barnes-Jewish Hospital, St. Louis, Missouri, USA, [2]Department of Pharmacy Practice, University of Health Sciences and Pharmacy, St. Louis, Missouri, USA, [3]Center for Clinical Excellence, BJC HealthCare, St. Louis, Missouri, USA, [4]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

Background. Hospital-acquired and ventilator-associated pneumonia (HAP/VAP) cause significant mortality. Guidelines recommend empiric broad-spectrum antibiotics followed by de-escalation (DE). This study sought to assess the impact of DE on treatment failure.

Methods. This single-center retrospective cohort study screened all adult patients with a discharge diagnosis code for pneumonia from 2016 to 2019. Patients were enrolled if they met predefined criteria for HAP/VAP ≥48 hours after admission. Date of pneumonia diagnosis was defined as day 0. Spectrum scores were calculated, and DE was defined as a score reduction on day 3 versus day 1. Patients with DE were compared to patients with no de-escalation (NDE). The primary outcome was composite treatment failure, defined as all-cause mortality or readmission for pneumonia within 30 days of diagnosis.

Results. Of 11 860 admissions screened, 1812 unique patient-admissions were included (1102 HAP, 710 VAP). Fewer patients received DE (876 DE vs 1026 NDE). Groups were well matched at baseline, although more patients receiving DE had respiratory cultures ordered (56.6% vs 50.6%, $P = .011$). There was no difference in composite treatment failure (35.0% DE vs 33.8% NDE, $P = .604$). De-escalation was not associated with treatment failure on multivariable Cox regression analysis (hazard ratio, 1.13; 95% confidence interval, 0.96–1.33). Patients receiving DE had fewer antibiotic days (median 9 vs 11, $P < .0001$), episodes of *Clostridioides difficile* infection (2.2% vs 3.8%, $P = .046$), and hospital days (median 20 vs 22 days, $P = .006$).

Conclusions. De-escalation and NDE resulted in similar rates of 30-day treatment failure; however, DE was associated with fewer antibiotic days, episodes of *C difficile* infection, and days of hospitalization.

Keywords. antibiotic de-escalation; hospital-acquired pneumonia; nosocomial pneumonia; spectrum score; ventilator-associated pneumonia.

Hospital-acquired pneumonia (HAP) is the most common hospital-acquired infection, accounting for 22% of all nosocomial infections [1]. Mortality rates for HAP and ventilator-acquired pneumonia (VAP) are high, ranging from 20% to 60% [2]. Inappropriate initial antimicrobial therapy is associated with increased mortality in patients with pneumonia, highlighting the need for initial broad-spectrum therapy [3]. The 2016 Infectious Diseases Society of America and American Thoracic Society guidelines recommend broad empiric coverage for patients with HAP and VAP, including treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (PSAR), followed by antibiotic de-escalation (DE) [2].

De-escalation refers to narrowing antimicrobial therapy, including complete cessation of antibiotics, to target likely pathogens while limiting activity against non-pathogenic flora [4]. Risks associated with prolonged and/or unnecessary antibiotic use are well documented. These include increased development of antimicrobial resistance, increased antibiotic adverse effects, and increased risk of *Clostridioides difficile* infection [4, 5]. Excess use of antibiotics has also been linked to more days in the intensive care unit (ICU) and a longer duration of hospitalization overall [6].

Defining DE for the purpose of research has proved challenging [7]. For this reason, many studies use qualitative measures, defining DE as the cessation of anti-MRSA coverage, anti-PSAR coverage, or both [8, 9]. However, these strategies neglect the full spectrum of activity provided by an antibiotic regimen, which can have important implications for both the human microbiome and local resistance patterns [10, 11]. In recent studies, quantitative methods (ie, spectrum scores) have

Received 29 June 2021; editorial decision 28 September 2021; accepted 11 October 2021; published online XX XX XXXX.

Correspondence: Dan Ilges, PharmD, Department of Pharmacy, Mayo Clinic Hospital, 5777 E Mayo Blvd, Phoenix, AZ 85054, USA (danilges@gmail.com).

Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab508

been developed that approximate the antimicrobial spectrum of a given agent, although the methodology for calculating such scores can become burdensome [12–14]. Gerber et al [15] developed a simple spectrum score, described as an antibiotic spectrum index (ASI). This method proved to be useful in assessing the impact of a stewardship intervention aimed at reducing the use of broad-spectrum antibiotics in the treatment of community-acquired pneumonia [15]. The purpose of this study was to evaluate the impact of DE, defined using a modified version of the ASI, on outcomes of patients with HAP/VAP.

METHODS

Study Design and Patient Population

This study was a retrospective cohort study of patients admitted to Barnes-Jewish Hospital, a 1300-bed academic medical center in St. Louis, Missouri, from January 1, 2016 to December 31, 2019. The study was approved by the Washington University institutional review board (IRB no. 2018801189) without the need to obtain informed consent. All adult admissions coded 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) discharge diagnosis code for pneumonia during the study period of interest were screened for inclusion (Supplementary Appendix). Patients were enrolled if they met predefined criteria for HAP or VAP, which included the following: (1) index date of infection onset ≥48 hours after hospital admission for HAP or ≥48 hours after initiation of mechanical ventilation for VAP, (2) chest radiograph completed within ± 24 hours of index pneumonia date, (3) active orders for either anti-MRSA or anti-PSAR antibiotics, and (4) at least 1 sign of infection, including a white blood cell count ≥11 or ≤4×10^9 cells/L, or temperature ≥38 or ≤36°C [8, 16–18]. To further support the diagnosis of pneumonia, a random sample of patients had their chest radiographs reviewed by an investigator (M. H. K.) blinded to group allocation, which demonstrated >95% agreement with the presence of radiographic infiltrates that could be consistent with pneumonia. Only the first eligible admission for a given patient was included. Patients were excluded if they discharged or died before day 3 or if they met criteria for pneumonia within 48 hours of hospital admission. The index date of pneumonia diagnosis was defined as day 0 (Figure 1).

All pharmacy-verified intravenous and oral antibiotic orders of interest were captured for each day of admission. Oral vancomycin, oral sulfamethoxazole/trimethoprim, and intravenous daptomycin orders were excluded. Spectrum scores were computed using a modified version of the ASI, adopted from Gerber et al [15] (Supplementary Table 1). Scores were calculated for antibiotics ordered on day 0 and for each successive day after

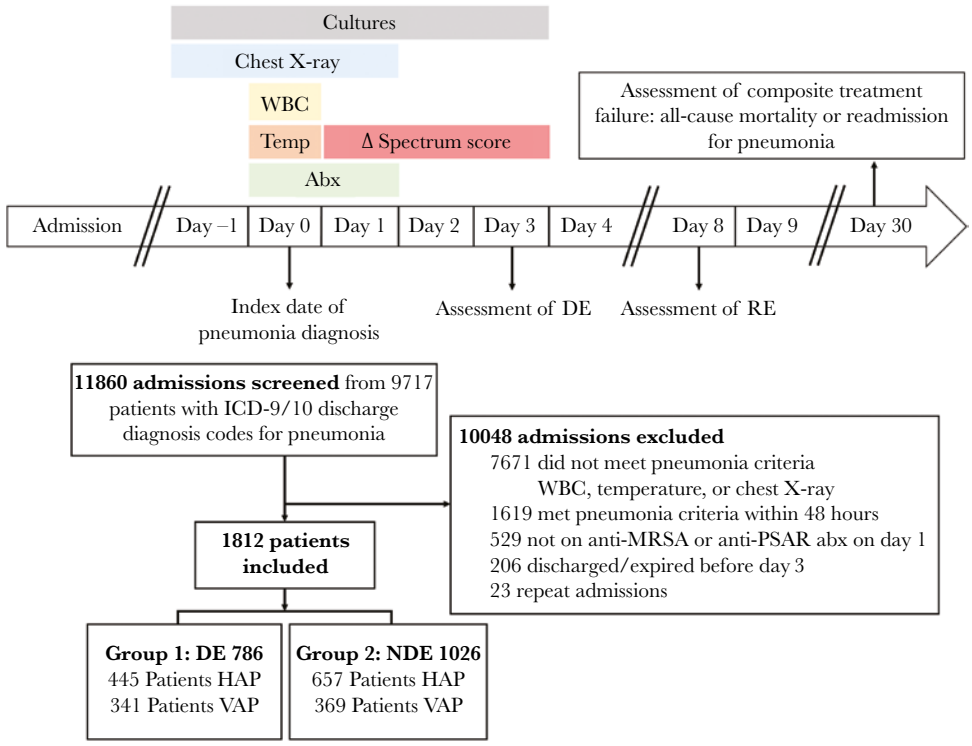

Figure 1. Study schematic and flow diagram. Abx, antibiotics; DE, de-escalation; HAP, hospital-acquired pneumonia; ICD, *International Classification of Diseases*; MRSA, methicillin-resistant *Staphylococcus aureus*; NDE, no de-escalation; PSAR, *Pseudomonas aeruginosa*; RE, re-escalation; Temp, temperature; VAP, ventilator-associated pneumonia; WBC, white blood cell count.

the index date of pneumonia diagnosis. When multiple antibiotics were ordered, the spectrum scores of the respective agents were summed into a composite score. For example, a patient on vancomycin and cefepime received a score of 12 (7 points for cefepime; 5 for vancomycin). 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 on admission. The Charlson comorbidity index (CCI) was calculated using methods previously described [19] to assess comorbidities at baseline. Orders for immunosuppressive medications were queried during the index admission and up to 30 days prior (Supplementary Appendix). Vasopressor orders queried included norepinephrine, vasopressin, and dobutamine. Creatinine clearance was estimated each day by the Cockcroft-Gault formula based on the highest serum creatinine value available.

Microbiologic data, including respiratory cultures, respiratory viral polymerase chain reaction tests, MRSA nasal culture swabs, and blood cultures, were collected from days −1 to 3 of index pneumonia diagnosis (Figure 1). Respiratory cultures were classified as sputum-like specimens, which included sputum and tracheal aspirates, and bronchoscopy specimens, which included bronchoalveolar lavage, washings, and brushings. Respiratory samples identified as positive for a likely pathogen excluded those with only yeast, fungal structural elements, and/or clinically insignificant flora. Blood cultures identified as positive for a likely pathogen excluded those with only coagulase-negative Staphylococci. Additional microbiological testing and reporting information is available in the Supplementary Appendix.

Outcomes

Patients were divided into 2 groups based on whether or not antibiotic DE occurred, which was defined as a reduction in spectrum score on day 3 compared with day 1 [13]. Patients with no change or an increase in spectrum score on day 3 compared to day 1 were classified as no de-escalation (NDE). Assessment of DE on day 3 was chosen to allow time for culture and susceptibility testing and for medical teams to respond to culture results.

The primary outcome was a composite of all-cause mortality or readmission for pneumonia within 30 days of pneumonia diagnosis. Secondary outcomes included the individual components of the primary outcome, as well as 14-day mortality, total hospital length of stay, ICU days, ventilator-free days, new vasopressor initiation, new onset *C difficile* infection up to 90 days postadmission, antibiotic days, treatment re-escalation, and development of acute kidney injury (AKI). Antibiotic days were calculated as the number of days that each patient had study antibiotics ordered from day 0 to 28. Treatment re-escalation was defined as an increase in spectrum score on or after day 8 to a value greater than the highest score on days 3 to 7 of hospitalization. Acute kidney injury was defined using serum creatinine according to the Kidney Disease—Improving Global Outcomes guidelines [20]. Baseline serum creatinine was defined as the maximum creatinine value on day 0.

Statistical Analysis

Baseline characteristics are presented using descriptive statistics. Categorical variables were compared using the χ^2 test. Continuous variables were assessed for normality and compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. The composite outcome of 30-day all-cause mortality or readmission for pneumonia was assessed using a log-rank test and Kaplan-Meier survival curve. To help control for confounding variables, predictors of the primary composite outcome were determined using a multivariable Cox regression analysis. De-escalation status, characteristics that were statistically significant on bivariate analysis ($P < .05$), and factors known to influence mortality were considered for inclusion in the model. Number of vasopressors (from 0 to 3) and ventilator status (yes/no) for days 0 through 3 were also included in the model, because these variables often influence clinical decision making with regards to antibiotic therapy. Predefined subgroup analyses were conducted for the primary outcome based on age, diagnosis, APACHE II score, sepsis diagnosis, and negative respiratory culture status.

We determined that 476 patients would be needed in each group to detect a 10% difference in the primary composite outcome of 30-day all-cause mortality or readmission for pneumonia, assuming a baseline incidence of 30%, with 90% power and a 2-sided alpha level of 0.05. Significance was defined as $P < .05$. All data were analyzed using IBM SPSS Statistics 25 for Windows.

RESULTS

A total of 11 860 admissions from 9717 unique patients were screened for inclusion (Figure 1). Of these, 10 048 admissions were excluded. The most common reasons for exclusion were failure to meet pneumonia criteria and meeting pneumonia criteria within 48 hours of admission. The final cohort consisted of 1812 specific patient-admissions, 786 (43.4%) of which were identified as DE. The median age was 62 years and 41.3% (749 of 1812) of patients were female. The median time from admission to diagnosis was 5 days, and 88.9% (1610 of 1812) of patients were in the ICU on day 0. A total of 60.8% of patients (1102 of 1812) had a diagnosis of HAP, 37.2% (410 of 1102) of which were ventilated, whereas the remaining patients had a diagnosis of VAP.

Overall, patient groups were well matched on baseline characteristics (Table 1). Patients in the DE group were more likely to have VAP compared to those in the NDE group (43.4% vs 36.0%; $P = .001$). Modified APACHE II scores were higher

Table 1. Baseline Characteristics

Characteristic	Total (n = 1812)	DE (n = 786)	NDE (n = 1026)	*P* Value
Age, years	62 [51–71]	62 [51–71]	61 [50–70]	.095
Female	749 (41.3)	317 (40.3)	432 (42.1)	.447
Race				.197
White	1314 (72.5)	556 (70.7)	758 (73.9)	
African American	409 (22.6)	194 (24.7)	215 (21.0)	
Other/unknown	89 (4.9)	36 (4.6)	53 (5.2)	
Height, m	1.7 [1.6–1.8]	1.7 [1.6–1.8]	1.7 [1.6–1.8]	.229
Weight, kg	81.2 [67.1–99.8]	80.7 [66.4–99.8]	81.5 [67.2–99.7]	.860
BMI, kg/m^2	27 [23–33]	27 [23–33]	27 [23–33]	.634
Modified APACHE II score	13 [9–17]	13 [10–17]	12 [9–16]	<.001
Location Diagnosed				.110
Medical ward	202 (11.1)	77 (9.8)	125 (12.2)	
ICU	1610 (88.9)	709 (90.2)	901 (87.8)	
Charlson comorbidity index	4 [2–6]	3 [2–6]	4 [2–6]	.045
Comorbid Conditions				
Heart failure	776 (42.8)	327 (41.6)	449 (43.8)	.357
Myocardial infarction	426 (23.5)	173 (22.0)	253 (24.7)	.188
Stroke	361 (19.9)	156 (19.8)	205 (20.0)	.944
Chronic obstructive pulmonary disease	334 (18.4)	134 (17.0)	200 (19.5)	.183
Liver disease	263 (14.5)	107 (13.6)	156 (15.2)	.341
Diabetes	495 (27.3)	210 (26.7)	285 (27.8)	.616
Renal disease	607 (33.5)	254 (32.3)	353 (34.4)	.350
Leukemia	198 (10.9)	71 (9.0)	127 (12.4)	.024
Lymphoma	83 (4.6)	41 (5.2)	42 (4.1)	.257
Cystic fibrosis	29 (1.6)	5 (0.6)	24 (2.3)	.004
Transplant Status				
Solid organ transplant (non-lung)	40 (2.2)	19 (2.4)	21 (2.0)	.595
Lung transplant	50 (2.8)	18 (2.3)	32 (3.1)	.286
Bone marrow transplant	95 (5.2)	35 (4.5)	60 (5.8)	.187
Immunosuppressive medications	248 (13.7)	84 (10.7)	164 (16.0)	.001
Sepsis	1100 (60.7)	469 (59.7)	631 (61.5)	.429
Septic shock	778/1100 (70.7)	327/469 (69.7)	451/631 (71.5)	.316
Number of vasopressors on day 0, mean ± SD	0.69 ± 0.84	0.66 ± 0.83	0.71 ± 0.85	.225
Lowest MAP on index date, mmHg[a]	75 [64–87]	74 [63–87]	76 [65–87]	.217
Neutropenia on day 0				
<1000 cells/μL	32 (1.8)	12 (1.5)	20 (1.9)	.498
<500 cells/μL	18 (1.0)	8 (1.0)	10 (1.0)	.927
T_{max} on index date, mean (SD)[a]	37.0 [36.7–37.5]	37.0 [36.7–37.6]	37.0 [36.7–37.4]	.019
WBC on index date[a]	11.5 [7.8–16.8]	11.5 [7.9–16.4]	11.6 [7.7–17.0]	.845
Dialysis	122 (6.7)	57 (7.3)	65 (6.3)	.440
Serum Creatinine, mg/dL[b]				
Admission	1.03 [0.75–1.45]	1.03 [0.72–1.46]	1.03 [0.77–1.44]	.446
Index date	0.99 [0.70–1.55]	0.95 [0.69–1.51]	1.02 [0.70–1.57]	.278
Creatinine Clearance, mL/min[b]				
Admission	62 [41–84]	61 [40–86]	62 [43–82]	.939
Index date	58 [39–82]	58 [37–85]	58 [39–80]	.814
Diagnosis				
HAP	1102 (60.8)	445 (56.6)	657 (64.0)	.001
Ventilated HAP	410 (37.2)	170 (38.2)	240 (36.5)	.673
VAP	710 (39.2)	341 (43.4)	369 (36.0)	.001
Days from admission to diagnosis (range)	5 [3–10] (2–168)	5 [3–10]	5 [3–10]	.271

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; DE, de-escalation; HAP, hospital-acquired pneumonia; ICU, intensive care unit; NDE, no de-escalation; MAP, mean arterial pressure; SD, standard deviation; WBC, white blood cell count.

NOTE: Results shown as no. (%) or median [interquartile range] unless otherwise indicated.

[a]T_{max} data only available for 1727 patients; WBC available for 1571 patients; MAP available for 1803 patients.

[b]Includes only patients without dialysis on admission or renal replacement therapy before day 0: 607 in DE group and 765 in NDE group.

among patients in the DE group (13 DE vs 12 NDE; $P < .001$), whereas CCI scores were higher among patients in the NDE group (3 DE vs 4 NDE; $P = .045$). Patients in the DE group were less likely to carry diagnoses of leukemia or cystic fibrosis or have received immunosuppressive medications in prior 30 days. There was no difference between groups based on transplant status, septic shock status, or neutropenia.

The most commonly ordered antibiotics were vancomycin, cefepime, meropenem, and linezolid (Table 2). The median spectrum score on day 1 was 14. Spectrum score trends over time are shown in Figure 2 and Supplementary Figure 1. Patients receiving DE experienced a 65% and 44% reduction in anti-MRSA and anti-PSAR therapies by day 3, respectively (Supplementary Figure 2). Significantly more patients in the DE group had respiratory bacterial cultures completed compared to those in the NDE group (56.6% vs 50.6%; $P = .011$). Accordingly, patients in the DE group were more likely to have respiratory cultures with a likely bacterial pathogen (50.8% vs 39.3%; $P < .001$) and/or clinically insignificant flora (19.3% vs 14.8%) compared to patients in the NDE group. The most common bacteria isolated were *S aureus*, *P aeruginosa*, and *Enterobacter* spp at 38.6%, 17.7%, and 9.5%, respectively.

Primary and secondary outcomes are shown in Table 3. There was no difference between groups in the primary outcome of 30-day composite treatment failure on bivariate analysis (35.0% DE vs 33.8% NDE; $P = .604$) or log-rank test (Supplementary Figure 3). There were also no differences in the individual components of the composite primary outcome, in-hospital mortality, 14-day all-cause mortality, readmission for any indication, or treatment re-escalation. However, patients in the DE group had fewer antibiotic days (median 9 vs 11, $P < .0001$), episodes of *C difficile* (2.2% vs 3.8%, $P = .046$), and hospital days (median 20 vs 22 days, $P = .006$). Patients in the DE group also spent less time in the ICU and on a ventilator compared to patients in the NDE group. In addition, there were consistent trends towards reduced AKI and initiation of renal replacement therapy in patients in the DE group compared to those in the NDE group.

Supplementary Table 2 shows the results of the multivariable Cox regression analysis. After controlling for confounding variables, including ventilator status and number of vasopressors by day, DE was not found to be a significant predictor of 30-day composite treatment failure (hazard ratio, 1.13; 95% confidence interval, 0.96–1.33). Statistically significant predictors of the primary outcome included modified APACHE II score, CCI, HAP status, septic shock, leukemia, and ventilator status on day 3. Attainment of respiratory specimens positive for a likely pathogen was also a statistically significant predictor of the primary outcome. The prespecified subgroup analysis did not identify any differences between groups in terms of 30-day all-cause mortality or readmission for pneumonia (Supplementary Table 3).

There were 423 patients still in the cohort (did not discharge or die) on day 27 (Figure 2, Supplementary Table 4). Of these, 243 of 423 (57.4%) remained on antibiotics of interest, with a median spectrum score of 9. Compared to the overall cohort, patients remaining on antibiotics on day 27 were numerically more likely to have leukemia (17.7% vs 10.9%), cystic fibrosis (2.9% vs 1.6%), coinfection (53.9% vs 34.0%), or receive immunosuppressive medications (21.0% vs 13.7%) (Supplementary Table 5).

DISCUSSION

In this large study of 1812 patients with HAP and VAP, antibiotic DE identified using changes in spectrum scores was not associated with 30-day composite treatment failure when compared to NDE. This lack of association persisted after controlling for confounding variables on multivariable Cox regression analysis and remained consistent among prespecified subgroups.

De-escalation is recommended following positive culture data (ie, narrowing to pathogen-directed therapy) and in clinically stable patients following negative cultures [2]. Despite these recommendations, DE may not occur. A recent retrospective study found that DE rates ranged from 2% to 35% following negative cultures in patients with pneumonia among 164 US hospitals from 2010 to 2015, although DE in this study was defined as cessation of both anti-MRSA and anti-PSAR therapies [21]. Similar to our study, a recent comprehensive systematic review and meta-analysis of 9 observational studies comprising 2128 patients with pneumonia in the ICU found that DE was associated with shorter hospital stay but had no discernable impact on mortality, although all studies were assessed as low-quality evidence [22]. Additional studies published after this meta-analysis have also found similar mortality outcomes among patients who received DE versus those who did not [13, 23, 24].

One difficulty in interpreting the DE literature is the wide range of definitions used, many of which are subjective and require chart review [22]. We opted to calculate spectrum scores using the modified ASI [15] and defined DE as a reduction in score on day 3 compared to day 1. Bohan et al [13] also used spectrum scores to define DE in a large retrospective cohort of veterans hospitalized with healthcare-associated pneumonia. Although the spectrum scoring methodology differed from ours, DE was similarly defined as a reduction in overall score. Likewise, there were no differences in clinical outcomes in patients who received DE versus those who did not [13]. In keeping both with traditional definitions of DE and antimicrobial stewardship program initiatives, patients in the DE group in our study had a 65% and 44% reduction in anti-MRSA and anti-PSAR therapies on day 3, respectively, contrasting starkly with the relatively unchanged utilization of these agents on day 3 in the NDE group.

Table 2. Antibiotic and Culture Data

Characteristic	Total (n = 1812)	DE (n = 786)	NDE (n = 1026)	*P* Value
Baseline Antibiotics on Day 1				
Vancomycin	1012 (55.8)	481 (61.2)	531 (51.8)	<.001
Cefepime	951 (52.5)	445 (56.6)	506 (49.3)	.002
Meropenem	616 (34.0)	269 (34.2)	347 (33.8)	.857
Linezolid	468 (25.8)	218 (27.7)	250 (24.4)	.104
Azithromycin	278 (15.3)	164 (20.9)	114 (11.1)	<.001
Piperacillin-tazobactam	112 (6.2)	58 (7.4)	54 (5.3)	.064
Ceftriaxone	91 (5.0)	69 (8.8)	22 (2.1)	<.001
Gentamicin	22 (1.2)	18 (2.3)	4 (0.4)	<.001
Antibiotics on Day 3				
Vancomycin	675 (37.3)	143 (18.2)	532 (51.9)	<.001
Cefepime	687 (37.9)	191 (24.3)	496 (48.3)	<.001
Meropenem	601 (33.2)	166 (21.1)	435 (42.4)	<.001
Linezolid	405 (22.4)	83 (10.6)	322 (31.4)	<.001
Azithromycin	167 (9.2)	44 (5.6)	123 (12.0)	<.001
Piperacillin-tazobactam	82 (4.5)	28 (3.6)	54 (5.3)	.084
Ceftriaxone	163 (9.0)	110 (14.0)	53 (5.2)	<.001
Gentamicin	13 (0.7)	3 (0.4)	10 (1.0)	.138
Number of Antibiotics				
Day 1 (mean ± SD)	2 [2–3]	2 [2–3] (2.57 ± 0.8)	2 [2–2] (2.04 ± 0.7)	<.001
Day 3	2 [1–2]	1 [1–2]	2 [2–3]	<.001
Anti-MRSA Antibiotic				
Day 1	1494 (82.5)	687 (87.4)	807 (78.7)	<.001
Day 3	1090 (60.2)	239 (30.4)	851 (82.9)	<.001
Antipseudomonal Antibiotic				
Day 1	1670 (92.2)	729 (92.7)	941 (91.7)	.418
Day 3	1371 (75.7)	408 (51.9)	963 (93.9)	<.001
Spectrum Score				
Admission	3 [0–13]	3 [0–13]	5 [0–12]	.766
Day 0	14 [11–16]	14 [11–16]	13 [12–16]	.786
Day 1	14 [12–16]	15 [12–18]	13 [10–15]	<.001
Day 3	12 [7–15]	7 [3–12]	15 [12–16]	<.001
Respiratory Samples Ordered	964 (53.2)	445 (56.6)	519 (50.6)	.011
Positive for likely respiratory pathogen	523/964 (54.3)	257/445 (57.8)	266/519 (51.3)	.043
MRSA Nasal Swab Sent	821 (45.3)	368 (46.8)	453 (44.2)	.258
Negative result	758/821 (92.3)	339/368 (92.1)	419/453 (92.5)	.841
Respiratory Specimen Type[a]				
Sputum-like	631 (65.5)	308 (69.2)	323 (62.2)	.023
BAL	464 (48.1)	207 (46.5)	257 (49.5)	.352
Respiratory clinically insignificant flora[b]	304 (16.8)	152 (19.3)	152 (14.8)	.011
Respiratory virus isolated	118 (12.2)	51 (11.5)	67 (12.9)	.494
Respiratory yeast isolated	220 (22.8)	93 (20.9)	127 (24.5)	.188
Respiratory mold isolated	23 (2.4)	5 (1.1)	18 (3.5)	.017
Respiratory bacteria isolated	430 (44.6)	226 (50.8)	204 (39.3)	<.001
Staphylococcus aureus	166 (38.6)	81 (35.8)	85 (41.7)	.215
Methicillin-susceptible	83 (50.0)	42 (51.9)	41 (48.2)	.641
Methicillin-resistant	83 (50.0)	39 (48.1)	44 (51.8)	.641
Vancomycin-intermediate	2 (1.2)	0	2 (2.4)	.497
Pseudomonas aeruginosa	76 (17.7)	42 (18.6)	34 (16.7)	.603
Enterobacter spp	41 (9.5)	25 (11.1)	16 (7.8)	.256
Escherichia coli	37 (8.6)	24 (10.6)	13 (6.4)	.117
Klebsiella spp	34 (7.9)	16 (7.1)	18 (8.8)	.503
Haemophilus spp	28 (6.5)	14 (6.2)	14 (6.9)	.779
Stenotrophomonas maltophilia	25 (5.8)	10 (4.4)	15 (7.4)	.195
Serratia marcescens	23 (5.3)	14 (6.2)	9 (4.4)	.412
Streptococcus pneumoniae	16 (3.7)	7 (3.1)	9 (4.4)	.472
Acinetobacter spp	12 (2.8)	4 (1.8)	12 (2.8)	.176

Table 2. Continued

Characteristic	Total (n = 1812)	DE (n = 786)	NDE (n = 1026)	*P* Value
Moraxella catarrhalis	8 (1.9)	5 (2.2)	3 (1.5)	.570
Proteus spp	7 (1.6)	6 (2.7)	1 (0.5)	.077
Streptococcus agalactiae	6 (1.4)	4 (1.8)	2 (1.0)	.486
Blood Culture Sent	1270 (70.1)	557 (70.9)	713 (69.5)	.527
Positive for likely bacterial pathogen	105/1270 (8.3)	42/557 (7.5)	63/713 (8.8)	.405
No respiratory or blood cultures sent day −1 to 3	366 (20.2)	151 (19.2)	215 (21.0)	.359
Coinfection during admission	616 (34.0)	262 (33.3)	354 (34.5)	.602

Abbreviations: BAL, bronchoalveolar lavage; DE, de-escalation; MRSA, methicillin-resistant *Staphylococcus aureus*; NDE, no de-escalation; SD, standard deviation.

NOTE: Results shown as no. (%) or median [interquartile range] unless otherwise indicated.

[a]Sputum-like = sputum, induced-sputum, and tracheal aspirates; BAL = washings and brushings.

[b]Clinically insignificant flora is only reported when other bacterial/fungal species are identified and reported in culture.

A drawback of retrospective research is the inherent selection bias present in treatment groups. For example, clinicians may not pursue DE in patients assessed as having a poor clinical status. In our study, patients with cystic fibrosis or leukemia were less likely to be de-escalated, although these represented small subgroups. However, strong predictors of mortality, such as septic shock and APACHE II score, were well balanced between treatment groups. Patients in the DE group were also more likely to have a positive respiratory pathogen obtained, which was shown to be a significant predictor of 30-day composite treatment failure. After controlling for these and other clinical parameters, such as ventilator status and number of vasopressors by day, there was no association between DE and the primary outcome.

One notable finding in this real-world study is the difference in respiratory culture data between comparison groups. Patients who had respiratory cultures ordered between days −1 and 3 were more likely to have a pathogen identified and to receive DE, regardless of respiratory specimen type. It is interesting to note that obtaining MRSA nasal culture swabs was not associated with DE; however, this could be due in part to variations in the timing of swabs (eg, swabbing on admission vs on suspicion of nosocomial pneumonia). Although these findings underscore the importance of obtaining respiratory samples, there was also no difference in composite treatment failure in patients with culture-negative pneumonia (either due to negative cultures or lack of cultures altogether). These data suggest that DE is safe in both circumstances and should be given strong consideration by clinicians managing patients with nosocomial pneumonia regardless of negative respiratory cultures.

The spectrum score-based methodology used in our study allows for objective, measurable, and reproducible identification of DE. Spectrum scores, such as the modified ASI, may also prove useful for benchmarking, both internally (for assessment of quality improvement projects) and externally (to compare to other institutions and identify areas of opportunity). For example, Yarrington et al [25] deployed the ASI to understand antimicrobial use across space and time within their institution, noting that utilization of broad-spectrum agents increases overnight and on weekends. Efforts are currently underway at our institution to incorporate the modified ASI into the electronic medical record, which would facilitate real-time quantification

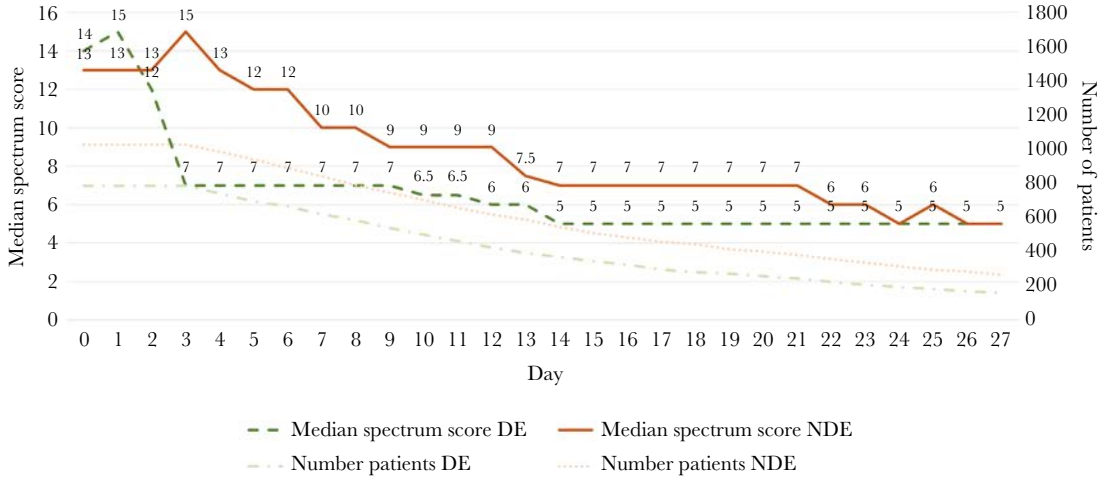

Figure 2. Median spectrum scores day 0 to 28. DE, de-escalation; ICU, intensive care unit; NDE, no de-escalation.

Table 3. Primary and Secondary Outcomes

Outcome	Total (n = 1812)	DE (n = 786)	NDE (n = 1026)	*P* Value
Primary Outcome				
Composite treatment failure[a]	622 (34.3)	275 (35.0)	347 (33.8)	.604
Secondary Outcomes				
30-day all-cause mortality	571 (31.5)	252 (32.1)	319 (31.1)	.660
Readmission for pneumonia within 30 days of day 0	65 (3.6)	28 (3.6)	37 (3.6)	.960
Readmission for pneumonia within 30 days of hospital discharge	97 (5.4)	37 (4.7)	60 (5.8)	.285
Readmission any within 30 days of hospital discharge	382 (21.1)	162 (20.6)	220 (21.4)	.667
Treatment re-escalation	416 (23.0)	191 (24.3)	225 (21.9)	.234
In-hospital mortality	517 (28.5)	212 (27.0)	305 (29.7)	.198
14-day mortality	407 (22.5)	180 (22.9)	227 (22.1)	.695
Days from index to expiration[c]	16 [8–58]	15 [7–53]	16 [8–59]	.165
Hospital Length of Stay, Days	21 [13–35]	20 [13–33]	22 [14–36]	.006
ICU days[d]	12.8 [7.0–22.0]	11.8 [6.9–20.2]	13.6 [7.1–23.9]	.004
Days ventilated[e]	10 [5–17]	9 [5–15]	10 [5–18]	.019
Ventilator-free days, percentage[e]	54.2 [28.6–72.7]	55.0 [30.0–72.7]	53.1 [26.7–72.8]	.496
Antibiotic days from day 0 to 28	10 [6–17]	9 [6–15]	11 [7–18]	<.001
AKI to day 21[b]				
Stage I	546 (35.5)	230 (34.4)	316 (36.4)	.423
Stage II	167 (10.9)	67 (10.0)	100 (11.5)	.352
Stage III	184 (12.0)	70 (10.5)	114 (13.1)	.112
AKI to Day 1 to Day 7[b]				
Stage I	421 (27.4)	169 (25.3)	252 (29.0)	.104
Stage II	118 (7.7)	47 (7.0)	71 (8.2)	.404
Stage III	132 (8.6)	52 (7.8)	80 (9.2)	.321
AKI to Day 8 to Day 14[b]				
Stage I	290 (18.9)	108 (16.2)	182 (21.0)	.017
Stage II	89 (5.8)	31 (4.6)	58 (6.7)	.090
Stage III	57 (3.7)	18 (2.7)	39 (4.5)	.065
AKI to Day 15 to Day 21[b]				
Stage I	151 (9.8)	55 (8.2)	96 (11.1)	.065
Stage II	48 (3.1)	22. (3.3)	26 (3.0)	.739
Stage III	28 (1.8)	10 (1.5)	18 (2.1)	.402
New RRT[b]	163 (10.6)	61 (9.1)	102 (11.8)	.098
Clostridioides difficile infection index to 90 days	56 (3.0)	17 (2.2)	39 (3.8)	.046
Additional vasopressor started days 4 through 7	202 (11.1)	75 (9.5)	127 (12.4)	.057

Abbreviations: AKI, acute kidney injury; DE, de-escalation; ICU, intensive care unit; NDE, no de-escalation; RRT, renal replacement therapy; SD, standard deviation.

NOTE: Results shown as no. (%) or median [interquartile range] unless otherwise indicated.

[a]30-day all-cause mortality or readmission for pneumonia within 30 days index pneumonia date.

[b]Of 1372 patients without dialysis on admission or receipt of RRT before day 0: 607 in DE group and 765 in NDE group.

[c]Of 857 patients with known expiration dates: 365 in DE and 492 in NDE.

[d]Of 1733 patients with any time in the ICU: 762 in DE and 971 in NDE.

[e]Of 1403 patients with any time ventilated: 626 in DE and 777 in NDE.

of antimicrobial burden and help identify patients that could be candidates for stewardship interventions.

Our study has several strengths. This is a large, contemporary cohort, which reflects current clinical practices and provides adequate power to minimize type II error. We screened patients using strict enrollment criteria for nosocomial pneumonia, notably excluding those who met these criteria too early in their hospital course. We also used a novel yet simple methodology to define antibiotic DE, which is easily reproducible and provides a comprehensive picture of the overall antimicrobial pressure on a patient's normal flora. Finally, we were able to collect and control for many confounding variables, including immunosuppressive medications, ventilator status by day, and number of vasopressors by day, utilizing a multivariable time-to-event regression analysis.

Our study also has limitations. First, as a single-center retrospective review, this study is subject to selection bias. Although our groups were relatively well matched at baseline, there may have been differences between groups that were unaccounted for, thereby limiting the capacity to determine causality. Furthermore, these results may not be generalizable to other institutions with different patient populations and/or practice models. For example, all patients in this cohort were receiving either anti-MRSA or anti-PSAR antibiotics on day

1, which may have made it relatively "easy" to be de-escalate. Second, using changes in spectrum scores to identify DE may lack specificity, because the difference in scores between 2 days can be influenced by minor changes in antibiotic orders (eg, one-time dose of aminoglycoside on day 1 and not continued on day 3). We also assessed antibiotic orders, not administrations. Although it is possible that some antibiotic orders were "counted" despite having never been administered, we considered such events rare enough to have minimal impact on the results. Furthermore, calculation of the modified ASI was consistent between treatment groups, and the differences in the groups remained evident over time as shown in Figure 2. Third, approximately one third of the patients in this study had coinfections, which may have impacted the ability to de-escalate; however, groups were well matched at baseline regarding number and type of coinfections (Supplementary Tables 6 and 7). Fourth, only a subset of vasopressors (norepinephrine, vasopressin, and dobutamine) were included. Fifth, most patients in this cohort were in the ICU, so results may not be generalizable to nosocomial pneumonia in noncritically ill patients. Finally, interpretation of chest radiographs and clinical criteria for establishing a diagnosis of pneumonia were determined by treating physicians at the time of hospital admission. Although this could introduce heterogeneity in terms of pneumonia diagnoses, we believe such heterogeneity reflects real-world circumstances and is therefore generalizable to other institutions.

CONCLUSIONS

Overuse of broad-spectrum antimicrobials remains a pressing public health problem. Although it is known that improper empiric antibiotic coverage is associated with increased mortality in patients with nosocomial pneumonia, excessive broad-spectrum antibiotic coverage carries risks of its own. Our findings suggest that antibiotic DE is not associated with composite treatment failure, but instead it may be associated with shorter hospitalizations and reduced rates of *C difficile* infection. Further studies are needed to fully understand the utility of spectrum score-based determinations of antibiotic DE.

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.

Acknowledgments

We thank Charles Goss for his consultation on the statistical analysis plan.

Financial support. M. H. K. is funded by the Barnes-Jewish Hospital Foundation.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Magill SS, O'Leary E, Janelle SJ, et al; Emerging Infections Program Hospital Prevalence Survey Team. Changes in prevalence of health care-associated infections in U.S. hospitals. N Engl J Med **2018**; 379:1732–44.
2. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis **2016**; 63:e61–111.
3. Marquet K, Liesenborgs A, Bergs J, et al. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. Crit Care **2015**; 19:63.
4. Masterton RG. Antibiotic de-escalation. Crit Care Clin **2011**; 27:149–62.
5. Dellit TH, Owens RC, McGowan JE Jr, et al; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis **2007**; 44:159–77.
6. Vaughn VM, Flanders SA, Snyder A, et al. Excess antibiotic treatment duration and adverse events in patients hospitalized with pneumonia: a multihospital cohort study. Ann Intern Med **2019**; 171:153–63.
7. Weiss E, Zahar JR, Lesprit P, et al; De-escalation Study Group. Elaboration of a consensual definition of de-escalation allowing a ranking of β-lactams. Clin Microbiol Infect **2015**; 21:649.e1–10.
8. Cowley MC, Ritchie DJ, Hampton N, et al. Outcomes associated with de-escalating therapy for methicillin-resistant *Staphylococcus aureus* in culture-negative nosocomial pneumonia. Chest **2019**; 155:53–9.
9. Kollef MH, Morrow LE, Niederman MS, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest **2006**; 129:1210–8.
10. Buising KL, Thursky KA, Robertson MB, et al. Electronic antibiotic stewardship–reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. J Antimicrob Chemother **2008**; 62:608–16.
11. Cook PP, Catrou P, Gooch M, Holbert D. Effect of reduction in ciprofloxacin use on prevalence of meticillin-resistant *Staphylococcus aureus* rates within individual units of a tertiary care hospital. J Hosp Infect **2006**; 64:348–51.
12. Madaras-Kelly K, Jones M, Remington R, et al. Development of an antibiotic spectrum score based on veterans affairs culture and susceptibility data for the purpose of measuring antibiotic de-escalation: a modified Delphi approach. Infect Control Hosp Epidemiol **2014**; 35:1103–13.
13. Bohan JG, Remington R, Jones M, et al. Outcomes associated with antimicrobial de-escalation of treatment for pneumonia within the veterans healthcare administration. Open Forum Infect Dis **2017**; 4:ofw244.
14. Yarrington ME, Moehring RW. Basic, advanced, and novel metrics to guide antibiotic use assessments. Curr Treat Options Infect Dis **2019**; 11:145–60.
15. Gerber JS, Hersh AL, Kronman MP, et al. Development and application of an antibiotic spectrum index for benchmarking antibiotic selection patterns across hospitals. Infect Control Hosp Epidemiol **2017**; 38:993–7.
16. Micek ST, Chew B, Hampton N, Kollef MH. A case-control study assessing the impact of nonventilated hospital-acquired pneumonia on patient outcomes. Chest **2016**; 150:1008–14.
17. Batlle HR, Klompas M; CDC Prevention Epicenters Program. Accuracy and reliability of electronic versus CDC surveillance criteria for non-ventilator hospital-acquired pneumonia. Infect Control Hosp Epidemiol **2020**; 41:219–21.
18. Andruska A, Micek ST, Shindo Y, et al. Pneumonia pathogen characterization is an independent determinant of hospital readmission. Chest **2015**; 148:103–11.
19. Glasheen WP, Cordier T, Gumpina R, et al. Charlson comorbidity index: ICD-9 update and ICD-10 translation. Am Health Drug Benefits **2019**; 12:188–97.
20. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract **2012**; 120:c179–84.
21. Deshpande A, Richter SS, Haessler S, et al. De-escalation of empiric antibiotics following negative cultures in hospitalized patients with pneumonia: rates and outcomes. Clin Infect Dis **2021**; 72:1314–22.
22. Ambaras Khan R, Aziz Z. Antibiotic de-escalation in patients with pneumonia in the intensive care unit: a systematic review and meta-analysis. Int J Clin Pract **2018**; 72:e13245.
23. Li H, Yang CH, Huang LO, et al. Antibiotics de-escalation in the treatment of ventilator-associated pneumonia in trauma patients: a retrospective study on propensity score matching method. Chin Med J **2018**; 131:1151–7.
24. Byoung Soo K, Sang Ho C, Younsuck K, et al. Safety of antimicrobial de-escalation for culture-negative severe pneumonia. J Crit Care **2019**; 54:14–9.
25. Yarrington M, Moehring RW, Anderson DJ, Wrenn R, Sarubbi C, Spivey J. Measuring empiric antibiotic spectrum patterns across space and time. Infect Control Hosp Epidemiol **2020**; 41:S2.