

Microbiology Comment Nudge Improves Pneumonia Prescribing

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Background. Systematic and behavioral interventions are needed to improve antibiotic use for common conditions like pneumonia.

Methods. Single pretest, post-test quasi-experiment in a 4-hospital health system in metropolitan Detroit, Michigan. Hospitalized patients treated with anti-methicillin-resistant *Staphylococcus aureus* and antipseudomonal antibiotics for respiratory infections from August 1, 2015, through January 31, 2016, and August 1, 2016, through January 31, 2017, were eligible for inclusion. Beginning in May 2016, respiratory cultures with no dominant organism growth and no *Pseudomonas* sp. or *Staphylococcus aureus* were reported by the clinical microbiology laboratory as “commensal respiratory flora only: No *S. aureus*/MRSA [methicillin-resistant *Staphylococcus aureus*] or *P. [Pseudomonas] aeruginosa*.” Before intervention, these were reported as “commensal respiratory flora.” The primary end point was de-escalation or discontinuation of anti-methicillin-resistant *Staphylococcus aureus* or antipseudomonal therapy. Secondary clinical and safety outcomes included nephrotoxicity and in-hospital, all-cause mortality.

Results. Two hundred ten patients were included in the study. De-escalation/discontinuation was more commonly performed in the intervention group (39% vs 73%, $P < .001$). After adjusting for APACHE II and Charlson Comorbidity Index, the intervention comment was associated with a 5.5-fold increased odds of de-escalation (adjusted odds ratio, 5.5; 95% confidence interval, 2.8–10.7). Acute kidney injury was reduced in the intervention phase (31% vs 14%, $P = .003$). No difference in all-cause mortality was detected between the groups (30% vs 18%, $P = .052$).

Conclusion. A simple, behavioral nudge in microbiology reporting increased de-escalation and discontinuation of unnecessary broad-spectrum antibiotics. This highlights the importance of clear, persuasive communication of diagnostic testing in improving antibiotic prescribing behaviors.

Keywords. antibiotic use; antimicrobial stewardship; microbiology; pneumonia; vancomycin.

Antibiotic prescribing for pneumonia comprises more than 30% of antibiotics in US hospitals on any given day [1]. Two broad-spectrum agents, vancomycin and piperacillin-tazobactam, account for nearly 20% of antibiotics prescribed for patients with community-onset lower respiratory tract infection (LRTI) [1]. The challenge of antibiotic prescribing for LRTI was compounded by health care-associated pneumonia (HCAP) criteria defined in the 2005 Infectious Disease Society of America and American Thoracic Society pneumonia guidelines. These HCAP

criteria had an unintended consequence of excessive use and continuation of empiric antibiotics targeting methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* [2–4]. Among patients admitted for suspected HCAP, Madaras-Kelly and colleagues noted approximately 67% and 57% were initiated on empiric therapy targeted toward *P. aeruginosa* and MRSA, respectively [5]. Of the patients who received anti-MRSA therapy but did not have MRSA identified, only 21.8% had anti-MRSA therapy discontinued by day 4, and only 15% of antipseudomonal agents were discontinued in patients with no *P. aeruginosa* isolated by day 4 [5].

Behavioral interventions for antimicrobial stewardship are gaining in prominence as clinicians develop a better understanding of the cultural influences on prescribing [6–8]. Microbiology results are a key decision point in the antimicrobial prescribing process. Therefore, behavioral strategies to improve the clarity of microbiology results may have an important role for antimicrobial stewardship programs. The language of microbiology results has previously been demonstrated to influence prescriber behavior, and some of these changes can be implemented with few additional resources [8–10]. Our

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objective was to assess the impact of a microbiology comment highlighting the absence of *Staphylococcus aureus*/MRSA and *P. aeruginosa* in respiratory culture. We hypothesized that implementing the microbiology comment would reduce antimicrobial therapy targeting MRSA and *P. aeruginosa*.

METHODS

Study Design

This quasi-experimental study was conducted over 2 study periods: a 6-month period before the intervention (August 1, 2015, through January 31, 2016) and a corresponding 6-month period following implementation of the intervention (August 1, 2016, through January 31, 2017). The reporting of respiratory commensal flora was changed across the health system in May 2016. The study population included all adult (>18 years) patients with respiratory cultures growing commensal flora only and receiving anti-MRSA and antipseudomonal antimicrobial therapy for an indication of respiratory tract infection according to medical record documentation. Respiratory specimens included in the study were sputum, tracheal aspirate, and mini-bronchoalveolar lavage. Antibiotic regimens included vancomycin or linezolid plus either cefepime, piperacillin/tazobactam, meropenem, or aztreonam. Antibiotic use for lower respiratory tract infection was determined from the indication listed with the antibiotic order, along with corroborating documentation by the treating provider in progress notes or discharge summary. The study was approved by the Henry Ford Health System Institutional Review Board with waiver of consent.

Study Data and Setting

The study was performed at a 4-hospital health system, the Henry Ford Health System, in metropolitan Detroit, Michigan. Data were extracted from electronic medical records using a standardized case report form. Patient characteristics, comorbid conditions, and multidrug-resistant organism risk factors were evaluated at the time of admission. Severity of illness, including APACHE II score, systemic inflammatory response syndrome (SIRS) criteria, and ventilator/vasopressor requirements, was recorded at the time respiratory cultures were reported to reflect patient status at the time of antibiotic decision-making. Microbiology data included timing of respiratory culture ordering, collection, and reporting.

The standard of care across the entire study period included a multidisciplinary antimicrobial stewardship program (ASP) with participation from pharmacy, microbiology, infectious diseases, and other specialties. Syndrome-based antimicrobial treatment guidelines were maintained by the ASP and available to all providers on the institutional intranet and within electronic medical record order sets. Infectious diseases (ID) pharmacists conducted prospective audit and feedback on selected antimicrobial use and microbiology results throughout

the entire study. In addition, prospective audit and feedback on antimicrobial use and microbiology results were routinely performed by the unit-based rounding clinical pharmacists according to ASP institutional guidelines. The microbiology laboratory adheres to Clinical Laboratory Standards Institute (CLSI) standards for testing and reporting [11]. “Commensal flora” respiratory culture results are reported for specimens with growth of organisms considered to be normal respiratory flora, including, but not limited to, *Neisseria*, *Corynebacterium*, and *Streptococcus*, and with no dominant growth of any single organism. Cultures with commensal flora plus dominant growth of an organism are resulted with both the name and susceptibility of the dominant organism plus commensal flora. Only cultures with solely commensal flora were included in the study population.

Intervention

In May 2016, a change in microbiology reporting on respiratory cultures growing commensal flora only was implemented at our institution to highlight the absence of MRSA and *P. aeruginosa*. Previously, the microbiology reporting at our institution stated “commensal respiratory flora” in the absence of predominant growth with typical respiratory pathogens. This comment was modified to “commensal respiratory flora only: No *S. aureus*/MRSA or *P. aeruginosa*.” The microbiology laboratory reported the modified comment on all respiratory cultures with mixed growth of normal flora, no dominant organism growth, and no significant amount of *Pseudomonas* sp. or *Staphylococcus aureus* identified by interpretation of colony morphology and hemolytic characteristics. The ASP created a 1-page written educational handout (Appendix) in conjunction with the reporting change. The ASP provided in-person education and provided the handout to the intensive care unit prescribers and pharmacists at department meetings. The handout was shared in the pharmacy department newsletter on multiple occasions. Provider education described that the goal of the reporting change was to highlight absence of pathogens that required anti-MRSA and antipseudomonal antibiotics and encouraged de-escalation.

Data and Outcome Measures

The primary outcome was de-escalation, defined as the proportion of patients who had anti-MRSA or antipseudomonal therapy discontinued or changed to a narrower-spectrum agent after the final culture result. Secondary outcomes included anti-MRSA and antipseudomonal agents used, duration of anti-MRSA and antipseudomonal therapy, and length of hospital and ICU stay. Safety end points included acute kidney injury (AKI), subsequent culture (any site) positive for a multidrug-resistant organism (MDRO) within same hospital stay, *Clostridium difficile* infection (CDI) within 30 days, and in-hospital all-cause mortality. AKI was defined as an increase in serum creatinine of ≥ 0.5 mg/dL on 2 consecutive daily laboratory draws or a decrease

of creatinine clearance by $\geq 50\%$ on 2 consecutive days after the respiratory culture result. MDRO was defined as an organism resistant to ≥ 3 classes of antimicrobials isolated anywhere on a patient within 14 days of the final respiratory culture and after the index course of antibiotics. All-cause in-hospital mortality was defined as death during the hospital stay for any reason. Given the quasi-experimental nature of the study and the lack of feasibility to utilize a control group, a negative control variable of appropriate use of deep venous thrombosis prophylaxis was evaluated. Appropriate DVT prophylaxis was defined as the use of heparin, low-molecular weight heparin, fondaparinux, or sequential compression devices in patients who were not on therapeutic anticoagulation or with a documented medical record problem of bleeding.

Statistical Analysis

The sample size of 210 patients was determined assuming an alpha of 0.05, beta of 0.15, and an anticipated effect size of 20% for antibiotic de-escalation [12]. Dichotomous data were analyzed by the Pearson χ^2 or Fisher exact test, as appropriate, and continuous data by Student *t* test or Mann-Whitney *U*, as appropriate. Logistic regression analysis was performed to evaluate variables independently associated with de-escalation while controlling for confounding factors. Variables with a *P* value of $<.2$ in bivariate analysis and with clinical rationale were considered for inclusion. In the final model, an adjusted odds ratio with a confidence interval that did not include 1.0 was

considered statistically significant. After the initial study results were observed, a post hoc analysis of characteristics associated with AKI was performed. All statistical analyses were performed using SPSS software, version 22.0 (IBM Inc., Armonk, NY).

RESULTS

During each study period, 105 patients were included. Baseline characteristics are presented in Table 1. Charlson Comorbidity Index at admission and APACHE II score at time of final culture suggested no major differences in patient characteristics between groups. Fifty percent of patients met criteria for sepsis, and 20% required mechanical ventilation. Similar proportions of patients in each study period had MDRO risk factors, but the specific risk factors varied. There was no difference between groups in the negative control variable, deep vein thrombosis prophylaxis use, suggesting a consistent standard of overall medication management and pharmacy services. Vancomycin was the empiric anti-MRSA therapy used in 100% of patients. Due to a cefepime shortage, there were differences in antipseudomonal therapy. Cefepime was used as the empiric antipseudomonal in 66% of pre-intervention patients, compared with 36% in the postintervention group. Piperacillin-tazobactam was used in 10% and 46% of patients in the pre- and postintervention groups, respectively.

The primary end point of de-escalation was achieved in 41 patients (39%) in the pre-intervention group and 77 patients

Table 1. Patient Characteristics

	Pre-intervention Group (n = 105)	Postintervention Group (n = 105)	<i>P</i> Value
Age, median (IQR), y	64 (54.5–75)	61 (51.5–73.5)	.138
Male sex, n (%)	55 (52)	59 (56)	.580
Charlson Comorbidity Index, median (IQR) ^a	3 (1–5)	2 (1–4)	.143
APACHE II, median (IQR) ^a	15 (10–20)	16 (10–20)	.491
≥ 2 SIRS criteria, n (%) ^a	58 (55)	47 (45)	.129
Vasopressor use, n (%) ^a	13 (12)	12 (11)	.831
Ventilation, n (%) ^{a,b}	22 (21)	21 (20)	.864
Concomitant nephrotoxins, n (%) ^c	81 (77)	73 (70)	.212
MDRO risk factors			
Antibiotics within 90 d ^d	44 (42)	53 (51)	.213
Hospitalized >48 h in 90 d	39 (37)	51 (49)	.094
Immunosuppressed ^e	21 (20)	25 (24)	.505
Pneumonia diagnosed >48 h after admission	19 (18)	19 (18)	1.0
Long-term care residence	16 (15)	7 (7)	.047
Outpatient dialysis	3 (3)	8 (8)	.214
Nonambulatory status ^f	6 (6)	3 (3)	.498

Abbreviations: IQR, interquartile range; MDRO, multidrug-resistant organism; SIRS, systemic inflammatory response syndrome.

^aEvaluated at the time of culture finalization.

^bFraction of inspired oxygen >50 or positive-end expiratory pressure >5 .

^cReceived nonsteroidal anti-inflammatory drug, acyclovir, angiotension-converting enzyme inhibitor or angiotension receptor blocker, aminoglycoside, amphotericin, methotrexate, or intravenous contrast dye for 1 day prior or any day after initial culture reporting while on broad spectrum antimicrobials.

^dReceived antimicrobials for >48 hours within 90 days.

^eTransplant patients, on immunosuppressive medications, presence of malignancy, chemotherapy within 3 months, CD4 count <350 , on steroid equivalent of prednisone 10 mg for at least 30 days, radiotherapy within 3 months.

^fBedridden or using a wheelchair.

(73%) in the intervention group ($P < .001$). MRSA therapy was de-escalated in 39 patients (37%), vs 75 patients (71%) in the pre and post groups ($P < .001$). Antipseudomonals were de-escalated in 34 (32%) patients in the pre-intervention group compared with 74 patients (70%) the intervention group ($P < .001$). After adjusting for APACHE II score ≤ 15 and Charlson Comorbidity Index < 3 , the intervention comment was associated with a 5.5-fold (95% confidence interval, 2.8–10.7) increased odds of de-escalation (Table 2).

The duration of anti-MRSA and antipseudomonal therapy was reduced from a median of 7 to 5 days ($P < .001$). There were no differences in median (IQR) intensive care unit length of stay (4 [3–8.3] vs 4.5 [2–7] days) or hospital length of stay (10 [5.8–14.3] vs 8 [5.8–12] days). No difference in all-cause mortality was detected between the groups (30% vs 18%, $P = .052$). Subsequent MDROs, isolated after the index course of anti-MRSA and antipseudomonal therapy, were isolated in 8 (8%) patients in the pre group vs 1 (1%) patient in the intervention group ($P = .035$). *Clostridium difficile* infection was identified in 2% and 3% of the pre- and postintervention group patients ($P = 1.0$).

The intervention comment was associated with a reduction in acute kidney injury in 33 (31%) pre-intervention patients compared with 15 (14%) intervention patients ($P = .003$). In post hoc regression analysis, the intervention comment was associated with a reduced risk of acute kidney injury (median [IQR], 0.3 [0.1–0.7]) after adjusting for APACHE II score > 15 , Charlson > 3 , and concomitant nephrotoxins.

DISCUSSION

Our study demonstrates that a simple behavioral intervention to more clearly communicate respiratory culture results for normal flora can impact prescribing and may reduce patient harm. The improved rate of antibiotic de-escalation resulted in a median 2-day reduction in anti-MRSA and antipseudomonal therapy. This study confirms previous experience. McBride and colleagues [12] at the University of Wisconsin observed an association between a respiratory culture comment specifying no MRSA and no *P. aeruginosa* with a reduction in anti-MRSA and antipseudomonal therapy. They concluded that the addition of

this comment may give prescribers the reassurance they need to de-escalate antimicrobial therapy [12]. The current study adds important patient outcome data, as we also observed an association with a reduced incidence of acute kidney injury. Overall, these findings emphasize the importance of microbiology lab communication as an antimicrobial stewardship strategy [6–10]. Interpretative comment modification represents a simple and cost-effective strategy that can be reproduced in most settings, including resource-limited settings.

We recognize the opportunity for more timely de-escalation, as intervention patients still received a median of 5 days of anti-MRSA and antipseudomonal therapy. Prescribers may have delayed or been less comfortable de-escalating therapy if the quality of the specimen was in question or if respiratory cultures were collected after antibiotics were initiated. The laboratory rejects respiratory culture specimens if a significant number of epithelial cells (oropharyngeal contamination) are identified on Gram-stain. Invasive diagnosis with bronchoalveolar lavage is not the standard of care in our institution, consistent with current national pneumonia guidelines [13]. Withholding antibiotics before collecting respiratory cultures is often not feasible in practice. Despite these potential limitations of culture specimens, we observed no worsening of patient clinical outcomes. In fact, our data suggest potential for improved outcome.

This study has some potential limitations. Quasi-experiments may be susceptible to maturation in practice or regression to the mean. It would have been impractical to implement a randomized design, as the 4-hospital system studied uses a centralized clinical microbiology laboratory, also precluding the use of a concurrent control group. We evaluated the same seasonal time period pre- and postintervention and included a negative control variable of DVT prophylaxis to assess overall quality of medication management to minimize these limitations. The postintervention group had fewer longer-term care facility residents; however, all patients in the study population were initiated on antipseudomonal and anti-MRSA therapy empirically and were subsequently eligible for de-escalation after a respiratory culture result for commensal flora. This difference was not associated with de-escalation in logistic regression and is unlikely to have impacted our study.

Table 2. Logistic Regression Analysis of Characteristics Associated With De-escalation

Variable	No De-escalation (n = 92), n (%)	De-escalation (n = 118), n (%)	P Value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No MRSA, no PA comment	28 (30)	77 (65)	<.001	4.3 (2.4–7.7)	5.5 (2.8–10.7)
Charlson < 3	32 (35)	76 (64)	<.001	3.4 (1.9–6.0)	2.9 (1.5–5.5)
APACHE II ≤ 15	36 (39)	73 (62)	.001	2.5 (1.4–4.4)	2.8 (1.4–5.4)
Long term care	9 (10)	14 (12)	.632	0.8 (0.3–2.0)	0.4 (0.1–1.0)
≥ 2 SIRS	53 (58)	52 (44)	.052	1.7 (1.0–3.0)	Not tested
Previous antibiotics	40 (44)	57 (48)	.486	0.8 (0.5–1.4)	Not tested
Hospitalization > 48 h	39 (42)	51 (43)	.904	1.0 (0.6–1.7)	Not tested

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; PA, *Pseudomonas aeruginosa*; SIRS, systemic inflammatory response syndrome.

CONCLUSION

This study highlights the importance of the way that microbiology results are communicated. Misinterpretation and gaps in the communication of microbiology results may inadvertently lead to suboptimal antibiotic prescribing. A simple respiratory culture comment nudge that specifies the absence of important organisms when reporting normal flora was associated with a reduction in broad-spectrum antibiotics targeting MRSA and *P. aeruginosa* and no worsening of length of stay or mortality. We also observed an association with reduced antibiotic harm. This study supports adoption of this simple behavioral strategy, with potential for substantial yield when incorporated into antimicrobial stewardship programs performing audit and feedback.

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