Predicting Antibiotic Resistance to Community-Acquired Pneumonia Antibiotics in Culture-Positive Patients With Healthcare-Associated Pneumonia

Karl J. Madaras-Kelly, PharmD, MPH1,4, Richard E. Remington, MS2,4, Vincent S. Fan, MD, MPH3,5, Kevin L. Sloan, MD6

1Clinical Pharmacy Service (119A), Veterans Affairs Medical Center, Boise, Idaho; 2Research Service, Veterans Affairs Medical Center, Boise, Idaho; 3Medical Service, Veterans Affairs Puget Sound Health Care System, Seattle, Washington; 4Department of Pharmacy Practice and Administrative Sciences, College of Pharmacy, Idaho State University, Meridian, Idaho; 5Department of Pulmonary and Critical Care Medicine, University of Washington School of Medicine, Seattle, Washington; 6Private Practice, Seattle, Washington.

OBJECTIVE: To develop and validate a model to predict resistance to community-acquired pneumonia antibiotics (CAP-resistance) among patients with healthcare-associated pneumonia (HCAP), and to compare the model's predictive performance to a model including only guideline-defined criteria for HCAP.

DESIGN: Retrospective cohort study.

SETTING: Six Veterans Affairs Medical Centers in the northwestern United States.

PATIENTS: Culture-positive inpatients with HCAP.

MEASUREMENTS: Patients were identified based upon guideline-defined criteria for HCAP. Relevant cultures obtained within 48 hours of admission were assessed to determine bacteriology and antibiotic susceptibility. Medical records for the year preceding admission were assessed to develop predictive models of CAP-resistance with logistic regression. The predictive performance of cohort-developed and guideline-defined models was compared.

RESULTS: CAP-resistant organisms were identified in 118 of 375 culture-positive patients. Of guideline-defined criteria, CAP-resistance was associated (odds ratio (OR) [95% confidence interval (CI)] with: admission from nursing home (2.6 [1.6-4.4]); recent antibiotic exposure (1.7 [1.0-2.8]); and prior hospitalization (1.6 [1.0-2.6]). In the cohort-developed model, CAP-resistance was associated with: admission from nursing home or recent nursing home discharge (2.3 [1.4-3.8]); positive methicillin-resistant Staphylococcus aureus (MRSA) history within 90 days of admission (6.4 [2.6-17.8]) or 91-365 days (2.3 [0.9-5.9]); cefepime exposure (1.8 [1.1-2.9]); recent intensive care unit (ICU) admission (1.6 [1.0-2.6]). Area under the receiver operating characteristic curve for the cohort-developed model (0.71 [0.65-0.77]) was significantly higher than for the guideline-defined model (0.63 [0.57-0.69]) (P = 0.01).


Healthcare associated pneumonia (HCAP) is defined as pneumonia that is present upon admission, and occurs in patients that have recently been hospitalized, reside in a nursing home, or have had other recent healthcare exposures. Practice guidelines developed by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), recommend strategies for the diagnosis and treatment of patients with HCAP.1 A premise of the guidelines is that recent healthcare exposure places patients at risk for infection due to multi-drug resistant (MDR) pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) or Pseudomonas aeruginosa. In addition to criteria utilized to define HCAP, the guidelines state that recent immunosuppression and antibiotic exposure are risk factors for pneumonia due to MDR pathogens. In contrast to the treatment of community-acquired pneumonia (CAP), the guidelines recommend empirical administration of antibiotics with activity against MRSA and Pseudomonas aeruginosa for all patients with HCAP.

We recently reported that antimicrobial resistance to CAP antibiotics (CAP-resistance) was identified in one-third of culture-positive patients with HCAP.2 Data regarding the predictive ability of the guideline-defined criteria specific to HCAP are limited.3 Evaluation and potential refinement of the criteria to identify patients at risk for MDR pathogens can aid in making antibiotic-related treatment decisions.

The purposes of this study are to: 1) develop and validate a model to predict CAP-resistance among patients with HCAP, and to compare the model's predictive performance to a model that includes...
traditional guideline-defined risk factors; and 2) develop models to predict recovery of pathogen-specific etiology (MRSA and *Pseudomonas aeruginosa*), and to compare the predictive performance of the pathogen-specific and CAP-resistance models.

**METHODS**

Patients with HCAP who were admitted to 6 Veterans Affairs Medical Centers (VAMC) in the northwestern United States between January 1, 2003 and December 31, 2008 were included in the retrospective cohort study. The cohort was identified utilizing medical records data extracted from the Veterans Integrated Service Network (VISN20) Data Warehouse. The Data Warehouse is a centralized open architecture relational database that houses medical and administrative records data for VISN20 patients. This research complies with all federal guidelines and VAMC policies relative to human subjects and clinical research.

Subjects were identified by the following pneumonia-related discharge International Classification of Diseases (ICD-9 CM) codes: 1) a primary diagnosis of 480-483; 485-487.0 (pneumonia); or 2) a primary diagnosis of 507.0 (pneumonitis), 518.8 (respiratory failure), or 0.38 (septicemia), and a secondary diagnosis of 480-483; 485-487.0. Eligibility required that patients received antibiotic therapy for pneumonia within 24 hours of admission, continue inpatient treatment for >24 hours, and meet any of the following guideline-defined criteria: 1) hospitalization during the preceding 90 days; 2) admission from a nursing home; 3) outpatient or home wound care, outpatient or home infusion therapy, or chronic hemodialysis.

In addition, patients not meeting guideline-defined criteria, who had frequent healthcare system exposure, defined as ≥12 Emergency Department, Medicine, or Surgery clinic visits within 90 days of admission, were also included. Patients were excluded if they were directly transferred from another hospital, or had pneumonia-related ICD-9 codes but received inpatient care for pneumonia in a non-VA hospital.

Study data included medical records for the year prior to admission for HCAP through 30 days afterwards. Data included: demographics; domicile preceding admission; healthcare utilization including diagnosis and procedure codes; inpatient medications administered, and outpatient prescription fills; vital signs; and laboratory test results, including cultures and susceptibilities.

Guideline-defined criteria for predicting CAP-resistance were similar to those used to identify the study cohort. Nursing home admission included patients who were directly admitted from a nursing home, skilled nursing facility, or domiciliary. Prior hospitalization ≥2 days within 90 days was calculated by summing the length of stay for all admissions during the preceding 90 days. Outpatient intravenous therapy, chronic hemodialysis, and wound care therapy was determined from medication administration records and relevant Current Procedural Terminology (CPT) or ICD-9 procedure codes for care administered within 30 days. Antibiotic exposure was defined as administration of ≥1 dose of antibiotic during inpatient care, or fill of an outpatient prescription for ≥1 antibiotic dose within 90 days preceding admission. Immunosuppression was defined as: human immunodeficiency virus (HIV) diagnosis; white blood cell (WBC) count of ≤2500 cells/mm³ within 30 days of admission; corticosteroid ingestion during prior admission, or outpatient prescription fills for a corticosteroid with quantity sufficient to last 14 days preceding admission; or inpatient ingestion of, or outpatient prescription fills for, transplant or rheumatologic-related immunosuppressants within 90 days preceding admission.

Additional variables assessed to predict CAP-resistance were obtained as follows. First, modifications of guideline-defined criteria were constructed. These included: direct nursing home admission, or recent nursing home stay preceding admission; total days of hospitalization within 90 days preceding admission; specific antibiotic exposures, including dates since last exposure preceding admission; and individual components of the immunosuppression criterion. Other cohort-developed variables included: demographics; substance use history; chronic comorbidity determined by individual and composite measures of Charlson score; pulmonary disease history (eg, bronchiectasis); type and frequency of outpatient visits; consecutive (≥2) prescription fills for chronic medications of interest; clinical and surveillance culture results preceding admission; admitting ward; vital signs; and relevant hematology and chemistry labs.

Sputum, blood, and bronchoscopy-collected cultures obtained within 48 hours after admission were assessed to determine specimen acceptability. Poor sputum specimens were defined by Gram stain quantitative results indicating >10 epithelial cells (EPI) per low power field (LPF), or in the absence of quantitative results, semi-quantitative results indicating 2-4+EPI. Single positive blood cultures with results indicating likely contaminants were considered poor specimens. All bronchoscopy-obtained specimens were considered acceptable. All cultures classified as poor specimens were excluded, and microbiology results were evaluated for the remaining specimens. Organisms thought to represent colonization or contamination were excluded: coagulase-negative (CN) *Staphylococcus*, *Enterococcus* sp, *Bacillus* sp, *Propionibacterium* sp, and *Candida* sp. Recovery of a potential pneumonia pathogen from ≥1 acceptable culture constituted a culture-positive admission.

CAP-resistance was determined for each isolate. CAP-resistance was defined as non-susceptibility to non-pseudomonal third generation cephalosporins (ceftriaxone or cefotaxime) or non-pseudomonal 8-
methoxy fluoroquinolones (moxifloxacin, gatifloxacin), the VA preferred agents for treatment of CAP.\textsuperscript{7} There were differences between facilities in susceptibility reporting criteria; therefore, the following approach was used to determine CAP-resistance. First, MRSA and \textit{Pseudomonas aeruginosa} isolates were classified as CAP-resistant. Second, susceptibility results were directly utilized to determine CAP-resistance if both antibiotic results were available. Third, if only a surrogate antibiotic from a class was reported, a representative antibiotic consistent with Clinical Laboratory Standards Institute reporting criteria was utilized.\textsuperscript{8} Finally, expert rules determined CAP-resistance for select potential pneumonia pathogens (eg, \textit{Haemophilus sp}) if antibiotic susceptibility results for both cephalosporin and fluoroquinolone classes were not reported.\textsuperscript{8-15} Presence of $\geq 1$ CAP-resistant isolate resulted in a CAP-resistant classification for an admission. MRSA and \textit{Pseudomonas aeruginosa} endpoints were defined in a similar manner. Only the first admission for each patient was utilized in the analysis.

The probability of CAP-resistance was predicted from guideline-defined criteria (guideline-defined model) with logistic regression. Next, non-guideline variables were classified as high, medium, or low interest for association with CAP-resistance. Variables were assessed for collinearity. A model of CAP-resistance was developed from variables of high interest. Guideline-defined criteria were omitted to allow consideration of more specific measures (eg, specific antibiotic exposures as opposed to receipt of antibiotics within the preceding 90 days) during this stage. Next, guideline-defined criteria, and subsequently variables of lesser interest, were added in an attempt to improve the model. Annual trends and plausible interactions were considered. Model selection was by Akaike’s Information Criterion (AIC).\textsuperscript{16} To promote model reliability, the final model was required to lack evidence of over-fitting in bootstrapped internal validation.\textsuperscript{17} The guideline-defined and cohort-developed models were compared by difference in area under receiver operating characteristic (aROC) curves. The model development process was repeated for MRSA and \textit{Pseudomonas aeruginosa} endpoints. Finally, to determine if the CAP-resistance model sufficiently predicted pathogen-specific MDR, the CAP-resistance model was re-estimated for MRSA and \textit{Pseudomonas aeruginosa} endpoints. Statistical analysis was performed with R version 2.10.0 (The R Foundation for Statistical Computing, Vienna, Austria).

\section*{RESULTS}

The cohort was comprised of 1300 patients with HCAP. Of these, 375 (28.8\% [26.4-31.4]) met culture-positive criteria for potential pneumonia pathogens. CAP-resistant organisms were identified in 118 (31.5\% [26.8-36.4]) patients within 48 hours of admission. CAP-resistant organisms included: MRSA (49.2\% [40.4-58.1]), \textit{Pseudomonas aeruginosa} (29.5\% [21.9-38.1]), Enterobacteriaceae (11.4\% [6.5-18.0]), Gram-negative non-enterics (8.3\% [4.2-14.4]), \textit{Streptococcus pneumoniae} (1.5\% [0.2-5.4]), and opportunistic organisms (eg, \textit{Mycobacterium spp}) (8.3\% [4.2-14.4]). Differences in select characteristics and exposures between culture-positive and culture-negative admissions, as well as CAP-resistant and CAP-sensitive admissions, were evident (Table 1).

Of the guideline-defined criteria, direct admission from a nursing home, prior hospitalization, and recent antibiotic exposure were associated with CAP-resistance (Table 2). The cohort-derived CAP-resistance model included 6 variables. Prior MRSA colonization or infection within 90 days preceding admission was strongly predictive of CAP-resistance. A composite variable consisting of direct admission from a nursing home or admission from the community after recent discharge from a nursing home was more predictive than direct admission from a nursing home alone. Exposure to cephalosporin antibiotics within the prior year was also predictive of CAP-resistance. Subcategorizing cephalosporins by class or by most recent exposure in 90-day increments did not improve the model. The remaining predictors in the model were guideline-defined infusion therapy criterion, diabetes, and intensive care unit (ICU) admission.

Of the guideline-defined criteria, direct admission from a nursing home was most predictive of MRSA HCAP (n = 57), followed by prior hospitalization and recent antibiotic exposure (Table 3). The cohort-developed model of MRSA HCAP included predictors common to the CAP-resistance model: direct admission from a nursing home or patients who were recently discharged from a nursing home, history of prior MRSA, and diabetes. Positive MRSA status within 90 days preceding admission exhibited the strongest prediction of MRSA HCAP. Exposure to anti-pseudomonal fluoroquinolones (ciprofloxacin and levofloxacin) within the prior year was also predictive of MRSA HCAP, however, exposure to 8-methoxy fluoroquinolone was not (crude odds ratio (OR) = 0.7 [0.3-1.4]; final model adjusted OR = 0.6 [0.2-1.2]). Exposure to third generation cephalosporins within the previous year was more predictive than other cephalosporin exposures, and more predictive than exposure times categorized in 90-day increments.

Of the guideline-defined criteria, only prior hospitalization within 90 days and admission from a nursing home were predictive of \textit{Pseudomonas aeruginosa} HCAP (n = 36) (Table 4). In the cohort-developed model of \textit{Pseudomonas aeruginosa} HCAP, \textit{Pseudomonas aeruginosa} was predicted by prior cephalosporin exposure within the preceding year, prior culture of \textit{Pseudomonas aeruginosa} from any anatomical source within the preceding year, and chronic steroid use of $\geq$ 10 mg/day prednisone equivalents. Again, the model was not improved by subcategorizing cephalosporin by class or...
by most recent exposure time. Finally, a negative annual trend in *Pseudomonas aeruginosa* HCAP was evident.

The cohort-developed model of CAP-resistance was re-estimated for MRSA and *Pseudomonas aeruginosa* endpoints. Only positive MRSA status within 90 days preceding admission was associated with both endpoints (OR = 8.7 [3.5–22.1] for MRSA; OR = 4.3 [1.4–12.2] for *Pseudomonas aeruginosa*). Direct or
TABLE 3. Comparison of Guideline-Defined and Cohort-Developed Models of MRSA HCAP

<table>
<thead>
<tr>
<th>Guideline-Defined Model of MRSA HCAP Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>AIC 316.3</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Intercept]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nursing home residence at time of admission</td>
<td>2.6</td>
<td>1.4-4.8</td>
<td>0.003</td>
<td></td>
<td>2.8</td>
<td>1.5-5.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization ≥2 days, ≤30 days prior to admission</td>
<td>1.8</td>
<td>1.0-3.5</td>
<td>0.075</td>
<td></td>
<td>2.0</td>
<td>1.1-3.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Antibiotic exposure ≤90 days prior to admission</td>
<td>1.6</td>
<td>0.9-3.3</td>
<td>0.143</td>
<td></td>
<td>1.4</td>
<td>0.9-2.1</td>
<td>0.507</td>
</tr>
<tr>
<td>Recent immunosuppression</td>
<td>0.6</td>
<td>0.3-1.3</td>
<td>0.244</td>
<td></td>
<td>0.8</td>
<td>0.4-1.7</td>
<td>0.507</td>
</tr>
<tr>
<td>Wound care therapy ≤30 days prior to admission</td>
<td>0.5</td>
<td>0.0-3.3</td>
<td>0.582</td>
<td></td>
<td>0.2</td>
<td>0.1-0.9</td>
<td>0.021</td>
</tr>
<tr>
<td>Infusion therapy ≤30 days prior to admission</td>
<td>0.9</td>
<td>0.4-2.0</td>
<td>0.733</td>
<td></td>
<td>2.1</td>
<td>1.0-4.7</td>
<td>0.234</td>
</tr>
<tr>
<td>Chronic hemodialysis ≤30 days prior to admission*</td>
<td></td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Value Variable OR 95% CI P Value

<table>
<thead>
<tr>
<th>Cohort-Developed Model of MRSA HCAP Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Intercept]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nursing home residence or discharge ≤180 days prior to admission</td>
<td>2.8</td>
<td>1.5-5.3</td>
<td>0.002</td>
</tr>
<tr>
<td>Positive MRSA status: ≤90 days prior to admission</td>
<td>1.7</td>
<td>1.1-2.9</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;90 days but ≤365 days prior to admission</td>
<td>1.4</td>
<td>0.9-2.1</td>
<td>0.507</td>
</tr>
<tr>
<td>Anti-pseudomonal fluoroquinolone exposure ≤365 days prior to admission</td>
<td>2.1</td>
<td>1.1-3.6</td>
<td>0.021</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.2</td>
<td>1.2-4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronic hemodialysis ≥30 days prior to admission</td>
<td>2.1</td>
<td>1.0-4.1</td>
<td>0.044</td>
</tr>
</tbody>
</table>

TABLE 4. Comparison of Guideline-Defined and Cohort-Developed Models of Pseudomonas aeruginosa HCAP

<table>
<thead>
<tr>
<th>Guideline-defined model of Pseudomonas aeruginosa HCAP Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>AIC 234.8</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hospitalization ≥2 days, ≤30 days prior to admission</td>
<td>2.5</td>
<td>1.1-6.0</td>
<td>0.034</td>
<td></td>
<td>1.9</td>
<td>1.0-3.9</td>
<td>0.037</td>
</tr>
<tr>
<td>Nursing home residence at time of admission</td>
<td>2.1</td>
<td>1.0-4.6</td>
<td>0.059</td>
<td></td>
<td>3.1</td>
<td>1.6-6.1</td>
<td>0.013</td>
</tr>
<tr>
<td>Chronic hemodialysis ≥30 days prior to admission</td>
<td>5.0</td>
<td>0.6-31.2</td>
<td>0.001</td>
<td></td>
<td>2.9</td>
<td>1.3-6.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Antibiotic exposure ≤90 days prior to admission</td>
<td>1.9</td>
<td>0.8-4.7</td>
<td>0.150</td>
<td></td>
<td>1.5</td>
<td>0.6-4.3</td>
<td>0.037</td>
</tr>
<tr>
<td>Infusion therapy ≤30 days prior to admission</td>
<td>1.8</td>
<td>0.7-4.2</td>
<td>0.172</td>
<td></td>
<td>2.4</td>
<td>1.2-5.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Recent immunosuppression</td>
<td>1.1</td>
<td>0.5-2.5</td>
<td>0.764</td>
<td></td>
<td>1.7</td>
<td>0.8-3.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Wound care therapy ≤30 days prior to admission*</td>
<td></td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Value Variable OR 95% CI P Value

<table>
<thead>
<tr>
<th>Cohort-developed model of Pseudomonas aeruginosa HCAP Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Intercept]</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cephalosporin exposure ≤365 days prior to admission</td>
<td>2.1</td>
<td>1.1-3.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Positive Pseudomonas aeruginosa culture ≤365 days prior to admission</td>
<td>3.3</td>
<td>1.4-7.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Chronic steroid dose of ≤10 mg/day prednisolone equivalents prior to admission</td>
<td>3.0</td>
<td>1.3-6.9</td>
<td>0.010</td>
</tr>
<tr>
<td>Year of study</td>
<td>0.8</td>
<td>0.7-1.0</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Value Variable OR 95% CI P Value

recent nursing home residence (OR = 2.4 [1.3-4.6]) and diabetes (OR = 2.4 [1.3-4.5]) were highly predictive of MRSA, but not *Pseudomonas aeruginosa* (OR = 1.8 [0.8-3.9] for nursing home residence; OR = 1.3 [0.6-2.7] for diabetes), respectively. Cephalosporin exposure preceding admission was highly predictive of *Pseudomonas aeruginosa* (OR = 4.0 [1.9-9.3]), but not with MRSA (OR = 1.1 [0.6-2.1]). In these models, all estimated odds ratios were >1.0, consistent with the cohort-developed model of CAP-resistance.

For each endpoint, the cohort-developed model was more predictive than the guideline-defined model (Table 5) (to view ROC curves see Supporting Figures 1 to 3 in the online version of the article.). The cohort-developed model of CAP-resistance re-estimated for pathogen-specific endpoints resulted in similar predictive performance. To assess performance of the cohort-developed models by facility, aROC was calculated for each of the 3 larger sites separately and for the 3 smaller facilities combined due to limited counts. Site specific aROC ranged from 0.652 to 0.762 for CAP-resistance, 0.725 to 0.815 for MRSA, and 0.719 to 0.801 for *Pseudomonas aeruginosa*. The cohort-developed model of CAP-resistance re-estimated for pathogen-specific endpoints resulted in similar predictive performance.

A nomogram for the cohort-developed model of CAP-resistance can provide the predicted probability of culturing a CAP-resistant organism for an individual patient (Table 6). Point scores assigned to levels of variables, are summed to obtain a total score, and the total score corresponds to a predicted probability of CAP-resistance. The prevalence of CAP-resistance (%) from highest to lowest quartile of predicted probability was 92.9, 58.8, 32.9, and 18.5, respectively.

DISCUSSION

In this study, select ATS/IDSA guideline-defined criteria predicted identification of CAP-resistant organisms in patients with HCAP. Admission from a nursing home was most predictive of CAP-resistant organisms, whereas recent hospitalization and antibiotic exposure were predictive to a lesser extent. There was weak evidence of associations between recent infusion and chronic hemodialysis criteria with MDR endpoints. Recent wound care and a composite definition of immunosuppression were not predictive of these endpoints.

The cohort-developed model resulted in improved prediction of CAP-resistance endpoints. Culture history, particularly history of MRSA within 90 days preceding admission, was a strong predictor of MDR endpoints. The MRSA history variable definition included cultures from all anatomical sources and nasal polymerase chain reaction surveillance results, the latter increasing in 2007-2008 due to the...
implementation of the VA MRSA initiative.18 This finding suggests that prior culture results should be considered when selecting empirical antimicrobial therapy, and the rapid proliferation of electronic medical records increases potential to utilize this information routinely. While the guideline-defined nursing home admission criterion was a strong predictor of CAP-resistance, admission from the community after recent MRSA colonization was strongly predictive of MRSA in defining the CAP-resistance endpoint. Both CAP-resistance and MRSA models included prior MRSA status, diabetes, and ICU admission, whereas cephalosporin exposure was common to the Pseudomonas aeruginosa and CAP-resistance models. Annual trends in CAP-resistance and MRSA recovery were not identified. The negative annual trend in Pseudomonas aeruginosa HCAP is unexplained and beyond the scope of this study. The percentage of culture-positive admissions with Pseudomonas aeruginosa HCAP averaged 12% in 2003-2006, but dropped to <5% in 2007-2008. A potential explanation is that identification and isolation of patients with MRSA, as a result of the VA-wide MRSA initiative, may have impacted Pseudomonas aeruginosa colonization by isolating patients co-colonized with these pathogens during prior healthcare exposures. This is consistent with the observation that when the cohort-derived CAP-resistance model was refit with the Pseudomonas aeruginosa endpoint, recent MRSA colonization was strongly predictive of Pseudomonas aeruginosa. Despite differences between variables in pathogen-specific and CAP-resistant models, the CAP-resistance model provided a similar degree of MRSA and Pseudomonas aeruginosa prediction. Finally, as a study purpose included developing best predictive models for each endpoint, and not merely identifying associations, there were other plausible models not reported.

Study strengths included use of the VISN20 Data Warehouse, which provided an integrated outpatient and inpatient medical record. This facilitated analysis of prior healthcare exposures and inpatient study endpoints. In addition, poor blood and sputum specimens and unlikely pneumonia pathogens were not included in establishing MDR endpoints. The variable set explored in regression modeling was extensive and detailed, and analysis included time and intensity-based components of the variables. Importantly, a standardized approach to regression modeling was specified in advance, which included identification of variables with high potential for association with MDR endpoints, model selection by AIC, re-evaluation of guideline-defined criteria and variables of lower interest, and bootstrapped internal model validation.19

Study limitations included the use of ICD-9 codes to establish a pneumonia diagnosis, which may lack sensitivity and specificity. However, an enhanced ICD-9-based algorithm superior to other claims-based

---

**TABLE 5. Area Under the Receiver Operator Characteristic Curve for Guideline-Defined and Cohort-Developed Regression Models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome Variable</th>
<th>Predictive Variables</th>
<th>aROC (95% CI)</th>
<th>Model Comparison</th>
<th>aROC Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CAP-resistance</td>
<td>Guideline-defined</td>
<td>0.630 (0.570, 0.691)</td>
<td>2-1</td>
<td>0.079 (0.018, 0.139)</td>
<td>0.011</td>
</tr>
<tr>
<td>2</td>
<td>CAP-resistance</td>
<td>Cohort-developed</td>
<td>0.709 (0.650, 0.768)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MRSA</td>
<td>Guideline-defined</td>
<td>0.638 (0.560, 0.712)</td>
<td>4-3</td>
<td>0.135 (0.057, 0.213)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>MRSA</td>
<td>Cohort-developed</td>
<td>0.733 (0.703, 0.844)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pseudomonas aeruginosa</td>
<td>Guideline-defined</td>
<td>0.680 (0.593, 0.768)</td>
<td>6-5</td>
<td>0.090 (−0.193, 0.193)</td>
<td>0.090</td>
</tr>
<tr>
<td>6</td>
<td>Pseudomonas aeruginosa</td>
<td>Cohort-developed</td>
<td>0.770 (0.683, 0.857)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MRSA</td>
<td>Cohort-developed from CAP-resistance model</td>
<td>0.755 (0.682, 0.828)</td>
<td>7-4</td>
<td>−0.018 (−0.067, 0.031)</td>
<td>0.467</td>
</tr>
<tr>
<td>8</td>
<td>Pseudomonas aeruginosa</td>
<td>Cohort-developed from CAP-resistance model</td>
<td>0.755 (0.685, 0.845)</td>
<td>8-6</td>
<td>−0.015 (−0.079, 0.049)</td>
<td>0.650</td>
</tr>
</tbody>
</table>

**Abbreviations:** aROC, area under the receiver operating characteristic; CAP, community-acquired pneumonia; CI, confidence interval; MRSA, methicillin-resistant Staphylococcus aureus.

---

**TABLE 6. Nomogram for Logistic Regression Model of CAP-Resistance**

### A. Scoring

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive MRSA status prior to admission</td>
<td>+100</td>
</tr>
<tr>
<td>≤30 days</td>
<td></td>
</tr>
<tr>
<td>&gt;30 days but ≤365 days</td>
<td>+45</td>
</tr>
<tr>
<td>Nursing home residence or discharge ≤180 days prior to admission</td>
<td>+45</td>
</tr>
<tr>
<td>Infusion therapy ≤30 days prior to admission</td>
<td>+35</td>
</tr>
<tr>
<td>Cephalosporin exposure ≤90 days prior to admission</td>
<td>+30</td>
</tr>
<tr>
<td>Diabetes</td>
<td>+30</td>
</tr>
<tr>
<td>Direct ICU admission upon hospitalization</td>
<td>+25</td>
</tr>
</tbody>
</table>

### B. Predicted Probability of CAP-Resistance

<table>
<thead>
<tr>
<th>Total Score</th>
<th>% Chance of CAP-Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>&lt;20</td>
</tr>
<tr>
<td>35-65</td>
<td>20-30</td>
</tr>
<tr>
<td>65-90</td>
<td>30-40</td>
</tr>
<tr>
<td>90-110</td>
<td>40-50</td>
</tr>
<tr>
<td>110-130</td>
<td>50-60</td>
</tr>
<tr>
<td>130-155</td>
<td>60-70</td>
</tr>
<tr>
<td>155-185</td>
<td>70-80</td>
</tr>
<tr>
<td>185-200</td>
<td>80-90</td>
</tr>
<tr>
<td>&gt;200</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAP, community-acquired pneumonia; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus.

*The minimum total score observed was 0 and the maximum total score observed was 230, which corresponded to 11% and 90% chance of CAP-resistance, respectively.*
developed pathogen-specific models in our study are the context of HCAP. Predictor variables in cohort- 
zation.21 Shorr et al., investigating a retrospective 
ment, nursing home residence, and prior hospitaliza-
guideline-defined criteria—prior antimicrobial treat-
625 consecutive ICU admissions determined that the 
studied. A prospective observational cohort study of 
ria to identify patients with MDR pathogens has been 
populations.

The predictive ability of the guideline-defined crite-
ria to identify patients with MDR pathogens has been 
studied. A prospective observational cohort study of 
625 consecutive ICU admissions determined that the 
guideline-defined criteria—prior antimicrobial treat-
ment, nursing home residence, and prior hospitaliza-
—were associated with recovery of MDR coloniza-

Shorr et al., investigating a retrospective 
cohort of 619 patients with HCAP, reported that 
recent hospitalization, nursing home residence, hemodi-
alysis, and ICU admission were associated with 
fishments caused by CAP-resistant organisms.22 This 
study did not report antimicrobial exposures. Our 
study complements these studies by evaluating existing 
HCAP guideline criteria, and identifying specific anti-
biotic exposure, prior culture data, comorbid illness, 
and immunosuppressive medications that are predic-
tive of MDR infection.

Studies comparing the bacterial etiology of patients 
with pneumonia in nursing homes relative to CAP, 
have demonstrated mixed results in recovery of Gram-
negative MDR pathogens, but generally increased 
MRSA pneumonia.3 Our study suggests that a nursing 
home stay in the last 6 months is associated with an 
increased risk for MRSA, but not Pseudomonas aeru-
ginosa, although this was limited by small sample 
size. Recent infusion therapy has not been previously 
reported to be associated with MDR pathogens in an 
HCAP population. In our study, this criterion was 
predictive of CAP-resistance in the cohort-developed 
model, but not in conjunction with other variables in 
the guideline-defined model. Predictors of pathogen-
specific HCAP are limited to an aforementioned single 
prior study, which identified recent hospitalization, 
nursing home residence, and ICU admission as risk 
factors for MRSA HCAP.22

Many studies have investigated risks for infection 
with MRSA and Pseudomonas aeruginosa outside of 
the context of HCAP. Predictor variables in cohort-
developed pathogen-specific models in our study are 
known risk factors for colonization or infection with 
these pathogens. For example, antecedent MRSA colo-
nization has been noted as a strong risk factor for 
MRSA infection, particularly pneumonia.23,24 Further, 
patients with diabetes and inhaled corticosteroid 
exposure are immunosuppressed and at increased risk 
for colonization with MRSA.25,26 Likewise, bronchio-
lar colonization and corticosteroid exposures are 
known risk factors for pneumonia due to Pseudomo-
nas aeruginosa.27

Many studies have identified prior antibiotic use as 
a risk factor for infections caused by MRSA and Pseu-
domonas aeruginosa. However, this criterion is exces-
sively broad and specific antimicrobial exposures carry 
different magnitudes of risk. Third generation cephalo-
sporins and anti-pseudomonal fluoroquinolones are 
commonly reported antibiotics associated with risk for 
MRSA infection, whereas 8-methoxy fluoroquinolones 
appear not to possess the same effect.28–31 Likewise, 
cephalosporins have been reported as risk factors for 
MDR Pseudomonas aeruginosa infections.32

Several areas of research involving HCAP MDR risk 
should be investigated. First, the predictive models 
developed in our and other studies should be evalu-
ated in larger, more diverse populations to establish 
generalizability. Second, empirical broad-spectrum 
antibiotic therapy in all patients with HCAP results in 
 overtreatment of many patients. To date, no reported 
models provided optimal performance for selecting 
empirical therapy for unstable ICU patients with 
HCAP, and many patients do not receive de-escalation 
therapy. Thus, models to identify patients with low 
probability of MDR pathogens upon admission and to 
aid in de-escalation are warranted. Finally, the nega-
tive trend in Pseudomonas aeruginosa HCAP requires 
confirmation and further study.

In conclusion, of the ATS/IDSA guideline-defined 
criteria for MDR, nursing home admission, recent 
hospitalization, and antibiotic exposure were predic-
tive of the recovery of CAP-resistant organisms. Alter-
native models primarily based on prior culture data, 
specific antibiotic exposures, and immunosuppression-
related variables improved predictive performance of 
HCAP associated with MDR.

This work was supported, in part, with resources and use of the Boise and Puget Sound Health Care System Veterans Affairs Medical Centers.

Disclosure: Karl J. Madaras-Kelly is employed full time by Idaho State University. The National Institute of Allergy and Infectious Diseases pro-
vided salary support for this study paid through Idaho State University (grant RO3AI074989-01A2). The National Institute of Allergy and Infection-
ous Diseases provided payment for statistical services on this study to Richard E. Remington, sub-contracted through Idaho State University 
(grant RO3AI074989-01A2). Vincent S. Fan is employed full time by the 
Department of Veterans Affairs, and receives grant support unrelated to 
the study from the Department of Veterans Affairs and the National Insti-
tutes of Health. He serves as a consultant for Uptake Medical Corpora-
tion. Kevin L. Sloan has no conflicts of interest to report.

References
Guidelines for the management of adults with hospital-acquired, ven-
tilator-associated, and healthcare-associated pneumonia. Am J Respir 


