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ORIGINAL RESEARCH

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

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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]); cephalosporin exposure (1.8 [1.1-2.9]); recent infusion therapy (1.9 [1.0-3.5]); diabetes (1.7 [1.0-2.8]); and intensive care unit (ICU) admission (1.6 [1.0-2.6]). Area under the receiver operating characteristic curve (aROC [95% CI]) 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]) ($P = 0.01$).

CONCLUSIONS: Select guideline-defined criteria predicted CAP-resistance. A cohort-developed model based primarily on prior MRSA history, nursing home residence, and specific antibiotic exposures provided improved prediction of CAP-resistant organisms in HCAP. *Journal of Hospital Medicine* 2012;7:195–202 © 2011 Society of Hospital Medicine.

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

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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.[4] 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.[1] 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/mm^3 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.[5]

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.[2,6] Organisms thought to represent colonization or contamination were excluded: coagulase-negative (CN) *Staphylococcus*, *Enterococcus* sp, *Bacillus* sp, *Proprionibacterium* 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.[7] There were differences between facilities in susceptibility reporting criteria; therefore, the following approach was used to determine CAP-resistance. First, MRSA and *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.[8] Finally, expert rules determined CAP-resistance for select potential pneumonia pathogens (eg, *Haemophilus sp*) if antibiotic susceptibility results for both cephalosporin and fluoroquinolone classes were not reported.[8–15] Presence of $\geq$1 CAP-resistant isolate resulted in a CAP-resistant classification for an admission. MRSA and *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).[16] To promote model reliability, the final model was required to lack evidence of over-fitting in bootstrapped internal validation.[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 *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 *Pseudomonas aeruginosa* endpoints. Statistical analysis was performed with R version 2.10.0 (The R Foundation for Statistical Computing, Vienna, Austria).

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]), *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]), *Streptococcus pneumoniae* (1.5% [0.2-5.4]), and opportunistic organisms (eg, *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 *Pseudomonas aeruginosa* HCAP (n = 36) (Table 4). In the cohort-developed model of *Pseudomonas aeruginosa* HCAP, *Pseudomonas aeruginosa* was predicted by prior cephalosporin exposure within the preceding year, prior culture of *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

TABLE 1. Cohort Demographics of HCAP Admissions

Characteristic	Culture-Negative Admissions (n = 925)	Culture-Positive Admissions (n = 375)	*P* Value	CAP-Sensitive Admissions (n = 257)	CAP-Resistant Admissions (n = 118)	*P* Value
Demographics						
Age (mean/SD)	71.9 (12.1)	71.4 (12.4)	0.44	70.4 (12.4)	72.9 (12.3)	0.07
Gender (% male)	97.1	98.8	0.07	98.4	99.2	1.00
Primary inclusion diagnosis (%)						
Pneumonia	93.1	85.9	<0.01	87.2	83.1	0.87
Aspiration pneumonitis with pneumonia pneumonia witpneumonia	1.5	4.3	0.02	4.6	3.3	0.48
Septicemia with pneumonia	2.6	6.2	<0.01	5.1	8.5	0.25
Respiratory failure with pneumonia	2.8	3.5	0.50	3.1	5.1	0.38
HCAP inclusion criteria (%)						
Nursing home residence	31.2	35.9	0.08	30.4	46.6	<0.01
Hospitalization of >2 days in last 90 days	58.7	57.6	0.73	52.1	62.7	0.06
Intravenous therapy in last 30 days	19.5	20.7	0.61	19.5	21.2	0.68
Outpatient wound care in last 30 days	2.7	2.7	1.00	3.1	1.7	0.73
Chronic dialysis in last 30 days	2.5	1.7	0.45	1.2	2.5	0.38
Hospitalization duration 0-2 days in last 90 days	10.2	11.2	0.57	12.5	5.9	0.22
>12 ED or clinic visits in last 90 days	44.1	44.6	0.86	44.0	41.5	0.74
Other guideline-defined MDR criteria (%)						
Antibiotics in last 90 days	63.8	61.6	0.47	57.2	66.1	0.11
Recent immunosuppression	19.3	23.9	0.53	24.1	22.0	0.70
Severity of illness (%)						
Admitted to the ICU	21.8	41.6	<0.01	26.3	38.6*	<0.01
Mechanical ventilation	5.6	12.7	<0.01	12.1	12.7	0.87
Comorbidity (%)						
Charlson comorbidity score (mean/SD)	4.3 (3.0)	4.3 (3.0)	0.85	4.1 (3.1)	4.5 (2.8)	0.20
Diabetes	33.8	29.2	0.10	27.2	39.0	0.07
Prior antibiotic use (%)						
Any cephalosporin	42.0	39.9	0.48	32.3	51.7	<0.01
Third generation cephalosporin	24.5	23.7	0.78	18.3	30.5	0.01
Anti-pseudomonal fluoroquinolone	28.5	28.4	1.0	23.3	37.3	0.02
8-Methoxy fluoroquinolone	20.1	23.9	0.10	24.1	24.5	1.00
Prior corticosteroid use (%)						
Systemic steroids (>10 mg/day prednisone)	11.1	13.2	0.28	11.3	16.1	0.24
Inhaled steroids	7.5	10.0	0.11	8.9	10.2	0.71
Prior MDR cultured (%)						
MRSA within <90 days	4.2	7.7	<0.01	2.7	15.3	<0.01
MRSA >90 days but <365 days	5.6	6.5	0.54	3.9	10.2	0.03
P. aeruginosa within ≤365 days	5.7	11.5	<0.01	5.8	19.5	<0.01

Abbreviations: CAP, community-acquired pneumonia; ED, emergency department; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MDR, multi-drug resistant; MRSA, methicillin-resistant *Staphylococcus aureus;* SD, standard deviation.

TABLE 2. Comparison of Guideline-Defined and Cohort-Developed Models of CAP-Resistant HCAP

Guideline–defined model of CAP–Resistant HCAP Variable	AIC 461.1			Cohort–Developed Model of CAP–resistant HCAP Variable	AIC 431.1		
	OR	95% CI	*P* Value		OR	95% CI	*P* Value
(Intercept)	NA	NA	NA	(Intercept)	NA	NA	NA
Nursing home residence at time of admission	2.6	1.6–4.4	<0.001	Nursing home residence or discharge ≤180 days prior to admission	2.3	1.4–3.8	0.002
Antibiotic exposure ≤90 days prior to admission	1.7	1.0–2.8	0.054	Positive MRSA status: ≤90 days prior to admission	6.4	2.6–17.8	<0.001
Hospitalization ≥2 days, ≤90 days prior to admission	1.6	1.0–2.6	0.066	>90 days but ≤365 days prior to admission	2.3	0.9–5.9	0.074
Infusion therapy ≤30 days prior to admission	1.5	0.8–2.8	0.173	Cephalosporin exposure ≤365 days prior to admission	1.8	1.1–2.9	0.019
Wound care therapy ≤30 days prior to admission	0.5	0.1–2.1	0.370	Infusion therapy ≤30 days prior to admission	1.9	1.0–3.5	0.044
Hemodialysis therapy ≤30 days prior to admission	1.8	0.3–11.2	0.497	Diabetes	1.7	1.0–2.8	0.044
Recent immunosuppression	0.9	0.5–1.6	0.670	Direct ICU admission upon hospitalization	1.6	1.0–2.6	0.053

Abbreviations: AIC, Akaike's Information Criterion; CAP, community-acquired pneumonia; CI, confidence interval; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* NA, not applicable; OR, odds ratio.

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

Guideline-Defined Model of MRSA HCAP Variable	AIC 316.3			Cohort-Developed Model of MRSA HCAP Variable	AIC 279.2		
	OR	95% CI	*P* Value		OR	95% CI	*P* Value
(Intercept)	NA	NA	NA	(Intercept)	NA	NA	NA
Nursing home residence at time of admission	2.6	1.4–4.8	0.003	Nursing home residence or discharge ≤180 days prior to admission	2.8	1.5–5.3	0.002
Hospitalization ≥2 days, ≤90 days prior to admission	1.8	1.0–3.5	0.075	Positive MRSA status: ≤90 days prior to admission	7.7	3.1–19.6	<0.001
Antibiotic exposure ≤90 days prior to admission	1.6	0.9–3.3	0.143	>90 days but ≤365 days prior to admission	1.4	0.5–4.1	0.507
Recent immunosuppression	0.6	0.3–1.3	0.244	Anti-pseudomonal fluoroquinolone exposure ≤365 days prior to admission	2.4	1.2–4.6	0.009
Wound care therapy ≤30 days prior to admission	0.5	0.0–3.3	0.582	Diabetes	2.2	1.2–4.3	0.012
Infusion therapy ≤30 days prior to admission	0.9	0.4–2.0	0.793	Chronic inhaled corticosteroids	2.8	1.1–7.1	0.031
Chronic hemodialysis ≤30 days prior to admission*	…	…	…	Third generation cephalosporin exposure ≤365 days prior to admission	2.1	1.0–4.1	0.040

Abbreviations: AIC, Akaike's Information Criterion; CI, confidence interval; HCAP, healthcare-associated pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus;* NA, not applicable; OR, odds ratio.
* Not included in model. No patient receiving chronic hemodialysis within 30 days of admission was identified as MRSA HCAP.

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

Guideline-defined model of *Pseudomonas aeruginosa* HCAP Variable	AIC 234.8			Cohort-developed model of *Pseudomonas aeruginosa* HCAP Variable	AIC 211.1		
	OR	95% CI	*P* Value		OR	95% CI	*P* value
(Intercept)	NA	NA	NA	(Intercept)	NA	NA	NA
Hospitalization ≥2 days, ≤90 days prior to admission	2.5	1.1–6.0	0.034	Cephalosporin exposure ≤365 days prior to admission	3.8	1.8–8.8	<0.001
Nursing home residence at time of admission	2.1	1.0–4.6	0.059	Positive *Pseudomonas aeruginosa* culture ≤365 days prior to admission	3.3	1.4–7.8	0.006
Chronic hemodialysis ≥30 days prior to admission	5.0	0.6–31.2	0.093	Chronic steroid dose of ≥10 mg/day prednisone equivalents prior to admission	3.0	1.3–6.9	0.010
Antibiotic exposure ≤90 days prior to admission	1.9	0.8–4.7	0.150	Year of study	0.8	0.7–1.0	0.069
Infusion therapy ≤30 days prior to admission	1.8	0.7–4.2	0.172				
Recent immunosuppression	1.1	0.5–2.5	0.764				
Wound care therapy ≤30 days prior to admission*	…	…	…				

Abbreviations: AIC, Akaike's Information Criterion; CI, confidence interval; HCAP, healthcare-associated pneumonia; NA, not applicable; OR, odds ratio.
* Not included in model. No patient receiving wound care therapy within 30 days prior to admission was identified as *Pseudomonas aeruginosa* HCAP.

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 nares polymerase chain reaction surveillance results, the latter increasing in 2007-2008 due to the

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

Model	Outcome Variable	Predictive Variables	aROC	(95% CI)	Model Comparison	aROC Difference	(95% CI)	*P* Value
1	CAP-resistance	Guideline-defined	0.630	(0.570, 0.691)	2-1	0.079	(0.018, 0.139)	0.011
2	CAP-resistance	Cohort-developed	0.709	(0.650, 0.768)				
3	MRSA	Guideline-defined	0.638	(0.560, 0.712)	4-3	0.135	(0.057, 0.213)	<0.001
4	MRSA	Cohort-developed	0.773	(0.703, 0.844)				
5	*Pseudomonas aeruginosa*	Guideline-defined	0.680	(0.593, 0.768)	6-5	0.090	(−0.193, 0.193)	0.090
6	*Pseudomonas aeruginosa*	Cohort-developed	0.770	(0.683, 0.857)				
7	MRSA	Cohort-developed from CAP-resistance model	0.755	(0.682, 0.828)	7-4	−0.018	(−0.067, 0.031)	0.467
8	*Pseudomonas aeruginosa*	Cohort-developed from CAP-resistance model	0.755	(0.665, 0.845)	8-6	−0.015	(−0.079, 0.049)	0.650

Abbreviations: aROC, area under the receiver operator 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

Variable	Score
Positive MRSA status prior to admission	
≤90 days	+100
>90 days but ≤365 days	+45
Nursing home residence or discharge ≤180 days prior to admission	+45
Infusion therapy ≤30 days prior to admission	+35
Cephalosporin exposure ≤365 days prior to admission	+30
Diabetes	+30
Direct ICU admission upon hospitalization	+25

B. Predicted Probability of CAP-Resistance*

Total Score	% Chance of CAP-Resistance
<35	<20
35–65	20–30
65–90	30–40
90–110	40–50
110–130	50–60
130–155	60–70
155–185	70–80
185–230	80–90
>230	>90

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.

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 discharge from a nursing home, in addition to direct admission from a nursing home, was also important.

Similarities in variables included in the pathogen-specific and CAP-resistance models reflect the importance 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

definitions of pneumonia was utilized.[4,20] Veterans may have received care at non-VA facilities impacting identification of all healthcare system exposures preceding admission. Data for microbial endpoints were obtained from sterile and non-sterile site cultures, and it was not possible to determine if the cultured organisms were truly pathogenic. While pathogen-specific endpoints were not affected, the use of expert rules in select cases to establish CAP-resistance may have impacted precision for this endpoint. It is also possible that refitting the cohort-developed CAP-resistance model for pathogen-specific endpoints resulted in optimistic aROC due to model over-fitting. Finally, the cohort was comprised of elderly males, and caution is warranted in extrapolating the results to other populations.

The predictive ability of the guideline-defined criteria 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 treatment, nursing home residence, and prior hospitalization—were associated with recovery of MDR colonization.[21] Shorr et al., investigating a retrospective cohort of 619 patients with HCAP, reported that recent hospitalization, nursing home residence, hemodialysis, and ICU admission were associated with infections 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 antibiotic exposure, prior culture data, comorbid illness, and immunosuppressive medications that are predictive 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 aeruginosa*, 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 colonization 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, bronchiolar colonization and corticosteroid exposures are known risk factors for pneumonia due to *Pseudomonas aeruginosa*.[27]

Many studies have identified prior antibiotic use as a risk factor for infections caused by MRSA and *Pseudomonas aeruginosa*. However, this criterion is excessively broad and specific antimicrobial exposures carry different magnitudes of risk. Third generation cephalosporins 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 evaluated 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 negative 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 predictive of the recovery of CAP-resistant organisms. Alternative models primarily based on prior culture data, specific antibiotic exposures, and immunosuppression-related variables improved predictive performance of HCAP associated with MDR.

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