Title

Simulated Adoption of 2019 Community-Acquired Pneumonia Guidelines Across 114 Veterans Affairs Medical Centers: Estimated Impact on Culturing and Antibiotic Selection in Hospitalized Patients

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Summary: Across VA facilities nationwide, universal adoption of 2019 ATS/IDSA community-acquired pneumonia guidelines would substantially reduce blood culturing, empiric anti-MRSA and antipseudomonal therapies, and over-coverage for MRSA and *P. aeruginosa* pneumonia but slightly increase respiratory cultures and under-coverage compared to previous practice.

ABSTRACT

Background: The 2019 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for community-acquired pneumonia (CAP) revised recommendations for culturing and empiric broad-spectrum antibiotics. We simulated guideline adoption in Veterans Affairs (VA) inpatients.

Methods: For all VA acute hospitalizations for CAP from 2006 – 2016 nationwide, we compared observed to guideline-expected proportions of hospitalizations with initial blood and respiratory cultures obtained, empiric antibiotic therapy with activity against Methicillin-resistant *Staphylococcus aureus* (anti-MRSA) or *Pseudomonas aeruginosa* (antipseudomonal), empiric "over-coverage" (receipt of anti-MRSA/antipseudomonal without eventual detection of MRSA/*P. aeruginosa* on culture), and empiric "under-coverage" (lack of anti-MRSA/antipseudomonal therapy with eventual detection on culture).

Results: Of 115,036 CAP hospitalizations over 11 years, 17,877 (16%) were admitted to an ICU. Guideline adoption would slightly increase respiratory culture (30% to 36%) and decrease blood culture proportions (93% to 36%) in hospital wards and increase both respiratory (40% to 100%) and blood (95% to 100%) cultures in ICUs. Adoption would decrease empiric selection of anti-MRSA (ward: 27% to 1%; ICU: 61% to 8%), and antipseudomonal (ward: 25% to 1%; ICU: 54% to 9%) therapies. This would correspond with greatly decreased MRSA over-coverage (ward: 27% to 1%; ICU: 56% to 8%), slightly increased MRSA under-coverage (ward: 0.6% to 1.3%; ICU: 0.5% to 3.3%), with similar findings for *P. aeruginosa*. For all comparisons $p < 0.001$.

Conclusions: Adoption of the 2019 CAP guidelines in this population would substantially change culturing and empiric antibiotic selection practices, with a decrease in over-coverage and slight increase in under-coverage for MRSA and *P. aeruginosa*.

INTRODUCTION

Community-acquired Pneumonia (CAP) is the most common infectious cause of death in the United States [1] and carries a significant and increasing economic burden [2]. Effective treatment requires timely administration of appropriate empiric antibiotic therapy [3], but the causative agent is rarely identified [4]. Without a reliable feedback mechanism to tailor empiric therapy decisions there remains much uncertainty into what empiric therapy is appropriate. Recognizing that the concept of health-care associated pneumonia (HCAP) [5,6] may have driven an increase in use of empiric antibiotic regimens with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* [7,8] without observed improvements in decision accuracy [9,10], the recently released 2019 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) practice guidelines for CAP retracted the HCAP category and recommended new indications for empiric anti-MRSA or antipseudomonal therapy as well as blood and respiratory cultures [11].

The implications of these guidelines are unknown. The aim of this study was to estimate the impact of the new ATS/IDSA CAP guidelines on culturing and empiric antibiotic selection practices in a large national cohort of patients hospitalized for CAP. We conducted a thought experiment [12] — "how would practice change if the guidelines were universally adopted?" — by comparing observed versus guideline-expected practices.

METHODS

Study Design, Setting and Participation

We conducted a retrospective cohort study of all immunocompetent patients hospitalized for CAP in the VA healthcare system from Jan 1, 2006 – Dec 31, 2016. We included adults (age ≥ 18) with hospitalization in acute inpatient wards following emergency department (ED) visits who underwent chest imaging and were diagnosed with CAP. We identified CAP diagnosis by a principal *International classification of disease-9* or 10 (ICD9/10) code for pneumonia, or secondary ICD9/10 code for pneumonia with a principal ICD9/10 code for sepsis and respiratory failure [13,14]. Patients were excluded if they had ED visits with chest imaging within the past 3 months, were not administered an antimicrobial within the first calendar day of hospitalization, or were immunocompromised (any of: AIDs, solid organ transplant, stem cell transplant, or neutropenia) [15], Data were accessed using Veterans Informatics and Computing Infrastructure (VINCI) [16].

The study was reviewed and approved, and waivers of consent and authorization were granted, by the University of Utah Institutional Review Board and the Research and Development Committee of the VA Salt Lake City Health Care System. Study data were not deidentified.

Measurements

Baseline comorbidities were defined by the presence of an outpatient ICD9/10 code within the past year prior to hospitalization [17]. Clinical risk factors for drug-resistant organisms including previous hospitalization within the prior 90 days, receipt of IV (parenteral) antibiotics within the prior 90 days, and detection of a positive respiratory culture for MRSA or *P. aeruginosa* within the prior year were abstracted using a previously validated approach in

VINCI [18]. We defined severe CAP as initial admission to an ICU rather than use severe CAP criteria due to the lack of unstructured chest imaging, and calculated the pneumonia severity index (PSI) score for context [19].

Observed practice

For each hospitalization, we determined whether initial respiratory or blood cultures were obtained within 24 hours before or after the time at ED presentation [20]. We extracted all antibiotics recorded in the bar code administration record within 6 hours prior to and 24 hours after initial ED presentation [18]. We classified "standard" therapy as the combination of a beta-lactam plus macrolide or tetracycline, or as monotherapy with a respiratory fluoroquinolone (moxifloxacin and levofloxacin); anti-MRSA therapy as any regimen that included vancomycin or linezolid; antipseudomonal therapy as any regimen that included piperacillin-tazobactam, cefepime, imipenem, meropenem, ticarcillin-clavulanate, ceftazidime, or an aminoglycoside.

Guideline-expected practice

We then examined the practice patterns that *would have* occurred if the 2019 CAP guidelines were applied at the time of hospitalizatiernon, summarized in **Table 1**. For the purposes of these analyses we assumed 100% guideline adoption. We treated recommendations for culturing and empiric antibiotic selection as independent, since physicians tend to adopt testing and treatment guidelines differently. In a secondary analysis we treated recommendations as dependent, which changed guideline-expected culturing to be contingent upon guideline-expected empiric antibiotic therapy instead of observed antibiotic practice.

For patients admitted to a hospital ward (non-ICU setting), we defined guideline-expected respiratory and blood cultures as present if there were anti-MRSA or antipseudomonal therapies initiated empirically on index hospitalization (observed empiric antibiotic use), prior respiratory isolation of MRSA or *P. aeruginosa* within 1 year, or clinical risk factors for resistant organisms including a history of hospitalization *and* receipt of IV antibiotics within 90 days. Guideline-expected blood and respiratory cultures were present in all ICU patients since ICU admission was used as a proxy for severe CAP. Guideline-expected anti-MRSA therapy was present if there was a history of MRSA isolation on respiratory culture within 1 year or ICU admission with clinical risk factors for resistant organisms. Guideline-expected antipseudomonal therapy was defined similarly. Guideline-expected "standard" therapy alone was present if there were no indications for anti-MRSA or antipseudomonal therapy. We additionally performed a secondary analysis using isolation from *any* culture source (not including MRSA nasal PCR) in the definition of guideline-expected antibiotic selection.

Statistical Analysis

Our primary analysis was a cross-sectional comparison of culturing and empiric antibiotic selection between observed and guideline-expected practices in subgroups initially admitted to the hospital ward and to the ICU. We reported proportions, by facility, of hospitalizations in which each practice was found. We used *Cochran-Maentel-Haentzel* tests [21] with stratification by facility to assess for statistically significant differences in observed-vs.-guideline expected proportions for each practice. We estimated the impact of guideline-expected culturing practices on MRSA and *P. aeruginosa* case detection rate using 2x2 contingency tables. Calculating the number of additional cases identified by additional guideline-expected

cultures was not possible in this study. We assessed the performance of clinicians to match empiric anti-MRSA or antipseudomonal therapy to detection on initial cultures ("bug-drug matching") using 2x2 contingency tables, similar to previous work [10]. We calculated sensitivity, specificity, and the diagnostic odds ratio as performance parameters. We defined empiric "under-coverage" as false negatives: the proportion of hospitalizations with MRSA/*P. aeruginosa* detected that did not receive anti-MRSA/antipseudomonal therapy. We defined empiric "over-coverage" as false positives: the proportion of hospitalizations with anti-MRSA/antipseudomonal therapy in which MRSA/*P. aeruginosa* was not detected on culture. In a secondary analysis, we assessed bug-drug matching in the subset of hospitalizations with cultures obtained, thus excluding those in which MRSA and *P. aeruginosa* could not be ruled out by negative culture.

We used appropriate summary measures to describe the populations admitted to the hospital ward and ICU. We used a two-tailed $p < 0.01$ as *a priori* level for significance. All statistical analyses were conducted using Stata version 15 (College Station, Texas) and figures were constructed using R version 3.5.3 (R Core Team, 2019) [22] with the ggplot2 package (Wickham, 2016) [23].

RESULTS

Across 114 VA hospitals over 11 years (Jan 1, 2006 – Dec 31, 2016) there were 115,036 hospitalizations for CAP meeting inclusion criteria, of which 17,877 (16%) were initially admitted to an ICU. The cohort was predominately elderly (median [IQR] age 70 [63 – 82]) men (97%) with a high burden of chronic disease (**Table 2**). There was a low prevalence of prior

respiratory isolation of MRSA (ward: 1%; ICU 1%) or *P. aeruginosa* (ward: 1%, ICU 2%). Clinical risk factors for resistant organisms were present in 5% of those admitted to a hospital ward and 8% of those admitted to an ICU.

Culturing and empiric antibiotic practices

Among patients admitted to a hospital ward, adoption of new CAP guideline recommendations would result in a slight increase in the proportion with respiratory cultures (30% to 36%) and substantial decrease in the proportion with blood cultures (93% to 36%) (**Figure 1**). Among patients admitted to the ICU (all severe CAP by our definition), both respiratory and blood culture proportions would increase (respiratory 40% to 100%; blood 95% to 100%). In the secondary analysis treating guideline-expected culturing as dependent upon universal adoption of antibiotic recommendations (**supplemental Figure 1**), guideline-expected respiratory and blood culture proportions on hospital wards would be 6% — substantially lower than the 36% seen in primary analysis (independent recommendations).

For admissions to hospital wards and ICUs guideline adoption would result in decreased proportions of both empiric anti-MRSA therapy (ward: 27% to 1%; ICU: 61% to 8%) and antipseudomonal therapy (ward: 25% to 1%; ICU: 54% to 9%) (**Figure 1**). Findings were similar, with slightly higher guideline-expected anti-MRSA and antipseudomonal therapy in a secondary analysis using prior isolation of resistant organism in *any* culture in the definition of guideline-expected antibiotic therapy (**supplemental Figure 2**). Differences were not substantially different across study years (**supplemental Figure 3**). For all comparisons $p < 0.001$.

Observed vs. guideline case detection

Among patients admitted to hospital wards, guideline-expected practice would be expected to substantially shift which patients are cultured. Guideline adoption would add cultures to some (respiratory: 25%; blood: 2%), remove cultures from others (respiratory: 19%; blood: 57%), and leave the rest unchanged (respiratory: 57%; blood: 41%) (**Figure 2**). Overall, 860 cultures (0.7 % of all cultures) that were positive for MRSA or *P. aeruginosa* would not have been obtained. This would correspond with missing 26% of MRSA and 36% of *P. aeruginosa* cases, including 45 cases of MRSA bacteremia, detected by observed culturing (0.8% of all ward admissions). It was not possible to assess how many additional cases may be identified by additional guideline-expected cultures.

Performance of empiric therapy selection (bug-drug matching)

Compared to eventual microbiological detection of MRSA and *P. aeruginosa* pneumonia (both 2% in hospital wards, 4% in ICUs) on initial cultures, guideline-expected therapy would result in greatly decreased MRSA over-coverage (ward: 27% to 1%; ICU: 56% to 8%) and slightly increased MRSA under-coverage (ward: 0.6% to 1.3%; ICU: 0.5% to 3.3%), with similar findings for *P. aeruginosa* (**Table 3**)**.** Guideline-expected use of anti-MRSA or antipseudomonal therapy was overall less sensitive, more specific, and more accurate (greater diagnostic odds ratios). When stratifying guideline-expected therapy by indication, a history of respiratory isolation was more accurate than healthcare exposure at predicting clinical infection. Findings

were similar in sensitivity analyses excluding patients in whom cultures were not sent (**supplemental Table 1**).

DISCUSSION

In this observational cross-sectional analysis of more than 100,000 CAP hospitalizations in VA facilities nationwide during 2006 – 2016, we found adoption of the new 2019 CAP guidelines would be expected to substantially change culturing and empiric antibiotic practices. Guidelines are expected to substantially reduce blood culturing and slightly increase respiratory culturing on hospital wards and increase all culturing in the ICU. In both hospital wards and ICUs, guideline adoption would be expected to substantially reduce usage of empiric anti-MRSA and antipseudomonal therapies. This reduction in broad-spectrum therapy would result in large decreases (>20%) in over-coverage and small increases (<2%) in under-coverage for MRSA and *P. aeruginosa*. Practice patterns following guideline adoption could differ from what was anticipated in several ways.

First, the guideline authors anticipated that the new recommendations should decrease unnecessary blood cultures in patients without severe CAP and increase appropriate respiratory cultures. Our findings show that the expected effects are congruent with this intention.. Presumably more frequently culturing the "right" patients would increase the overall diagnostic yield [24–26]. However, we estimated that 370 (26%) of MRSA and 479 (36%) of *P. aeruginosa* cases would be "missed" by guideline recommended culturing on hospital wards, including 45 (11%) of cases of MRSA bacteremia. We were unable to calculate how many additional cases might be identified by additional cultures.

Shifting culture practice, while unlikely to directly impact most (~99%) patients, could impact several important health-system level activities via alterations in sampling [27]. With prevalence already low, missing cases of resistant CAP could compromise efforts at local risk factor identification and validation, which generally requires at least 30 cases per year [28]. Since isolation and resistance patterns in CAP are dependent upon the source (respiratory vs. blood) [29], local antibiograms could shift without actual changes in true organism prevalence. As a consequence of both of these processes the predictive utility of previously developed risk-scores for resistant CAP (e.g. DRIP score [30]) could also shift in unpredictable ways. This highlights the tension between the goals of reducing unnecessary culturing and improving surveillance.

We found that guideline adoption would match the stated intention of substantially decreasing use of empiric anti-MRSA and antipseudomonal therapies, but perhaps more than anticipated. Since the introduction of the HCAP concept in 2005 [5] use of anti-MRSA and antipseudomonal regimens has more than doubled [7,10]. Our findings confirm a large sustained increase in observed use of anti-MRSA and antipseudomonal therapies and suggest that the 2019 guidelines would accomplish the stated intent to curb this growth and then some. Use of anti-MRSA and antipseudomonal regimens could fall far below the pre-2005 levels. This implies a small but significant absolute increase (~2%) in the rate of empiric under-coverage with a large absolute decrease (26%) in over-coverage for MRSA/*P. aeruginosa* pneumonia.

Weighing the consequences of changes in under-coverage and over-coverage is complex, particularly if those patients that would experience under-coverage are sicker. Increased mortality associated with initial under-coverage for patients presenting with septic shock [31] and corresponding sepsis guideline recommendations [32,33] support more frequent use of broad-spectrum antibiotics [31]. However, even patients admitted to ICUs may have just as great

a risk of harm from over-coverage with these agents, including renal toxicity and secondary infection [34]. In pneumonia, anti-MRSA and antipseudomonal therapy has not been associated with improved outcomes in observational cohort studies [8,10], or pre-post analyses of antimicrobial stewardship programs [35]. For the VA population, we previously failed to establish a benefit of empiric anti-MRSA therapy, even when used in those with elevated risk for MRSA pneumonia [36]. In settings of diagnostic uncertainty such as this, providers must weigh risks and benefits. The work of Kahneman, Tversky, and others has demonstrated that humans have difficulty thinking probabilistically and tend to overweight possible negative outcomes [37]. Fear is a powerful, sometimes useful, component of clinical decision making [38,39], and influences bedside application of clinical decision guidelines [40]. The magnitude of change in empiric antibiotic practices that we find the 2019 CAP guidelines suggest raises an important unanswered question: what is the optimal balance between over-coverage and under-coverage with broad-spectrum antibiotics that will maximize benefit and reduce harms, and to what degree if any should this vary across settings?

Limitations

This study has several important limitations to consider. As this was a "thought experiment", we did not evaluate changes in health outcomes, but only expected changes in clinical practice and explicitly ignored the variable clinical application of guideline recommendations that might be seen in a prospective interventional trial. We chose to simulate 100% ("complete") guideline adoption to most closely examine the theoretical implications of the guideline statement. Our results provide food for thought rather than a forecast. Providers are also influenced by the Surviving Sepsis Guideline recommendations for blood cultures in all

patients and timely initiation of broad-spectrum IV antibiotics [32,33]. This may partially explain high observed proportions of combined anti-MRSA and antipseudomonal therapy (e.g. "vanc-zosyn" [the combination of vancomycin and piperacillin-tazobactam]). We explicitly did not address impacts of MRSA nasal PCRs given their current variability in turnaround times. This study relies upon structured data readily available in the electronic health record in the VA patient population and there are many uncaptured factors, values, and preferences that are appropriately used in conjunction with guidelines at the bedside for clinical decision making. As in many studies on CAP, accurate selection of CAP cases is challenging. We relied on discharge diagnosis codes to select CAP cases which may have included cases in which there was a different initial working diagnosis (i.e. undifferentiated sepsis) that drove observed practice. Our study period (2006 – 2016) while relatively recent may not represent practice patterns in more recent years (2017-2020). We explicitly ignored the guideline recommendation to develop "locally validated risk factors" to predict MRSA or *P. aeruginosa* CAP since validating such factors was not feasible in this dataset. It remains to be seen how well organizations will be able to identify and validate local risk factors in practice and future research will be needed to evaluate the impact of this strategy on clinical outcomes. Lastly, the VA population is unique in several ways, most notably in the predominance of older men, so our findings may not generalize to other populations or settings.

Our study has several notable strengths including a large nationwide sample size, well validated measurements of patient characteristics, culturing, and antibiotic practices, and high proportion of objectively documented risk factors for drug-resistant pneumonias due to the single-system nature of the VA.

CONCLUSION

Adoption of the 2019 ATS/IDSA CAP guidelines across the VA system would be expected to decrease blood culturing in non-ICU patients and substantially decrease the use of empiric broad-spectrum antibiotics. These changes would correspond with decreased rates of over-coverage and increased rates of under-coverage with overall slightly improved accuracy of empiric antibiotic selection for microbiological detection. These findings suggest that hospital administrators, antibiotic stewardship directors, and health systems should carefully consider how to implement the new guidelines depending upon local priorities. Conducting simulations such as ours to estimate the degree of change called for by new recommendations could be a useful tool for future guideline development.

NOTES

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Critical revision of the manuscript for important intellectual content: all authors

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TABLES

Table 1. Summary of guideline-expected culturing and empiric antibiotic inpatient practice for community acquired pneumonia.

Recommended Practice	Non-severe CAP (~ Ward)	Severe CAP (~ ICU)
Culturing		
Obtain respiratory cultures[a]	No recommendation for/against *except for any of:* a. empiric treatment for MRSA or PA[b] b. Prior respiratory isolation of MRSA or PA c. Clinical risk factors for resistant organisms[c]	routine
Obtain blood cultures	suggest against routinely obtaining *except for any of:* a. empiric treatment for MRSA or PA[b] b. Prior respiratory isolation of MRSA or PA c. Clinical risk factors for resistant organisms[c]	routine
Empiric antibiotic selection		
Standard	routine	routine
Add anti-MRSA	Prior respiratory isolation of MRSA	Prior respiratory isolation of MRSA *or* Clinical risk factors for resistance organisms[c]
Add anti-PA	Prior respiratory isolation of PA	Prior respiratory isolation of PA *or* Clinical risk factors for resistant organisms[c]
Add anti-MRSA & anti-PA	Prior respiratory isolation of MRSA & PA	Prior respiratory isolation of MRSA & PA *or* Clinical risk factors for resistant organisms[b]

Adapted from 2019 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for community-acquired pneumonia. Metlay JP, et al. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67. DOI: 10.1164/rccm.201908-1581ST

[a] respiratory culture indicates gram stain and culture of sputum, tracheal aspirate, bronchoalveolar lavage specimens, and pleural fluid.

[b] Empiric treatment with anti-MRSA or anti-PA therapy selected for some other reason is listed as an indication for obtaining cultures

[c] Clinical risk factors for resistant organisms include the combination of hospitalization within preceding 90 days and receipt of IV antibiotics (not necessarily during the prior hospitalization) within preceding 90 days

CAP = community acquired pneumonia ICU = intensive care unit. MRSA = methicillin resistant *Staphylococcus aureus*. PA = *Pseudomonas aeruginosa.*

Table 2. Characteristics of hospitalizations for CAP

Characteristic	Hospital Ward (N = 97,159)	ICU (N = 17,877)
Comorbidities		
Age, median (IQR), years	71 (63 - 82)	69 (62 - 80)
Male sex, n (%)	93,859 (97%)	17,302 (97%)
Pulmonary disease, n (%)	43,455 (45%)	8,658 (48%)
Congestive heart failure, n (%)	17,856 (18%)	4,246 (24%)
Coronary artery disease, n (%)	41,609 (43%)	8,254 (46%)
Renal disease, n (%)	14,947 (15%)	3,114 (17%)
Liver disease, n (%)	1,973 (2%)	573 (3%)
Cancer, n (%)	22,141 (23%)	3,965 (22%)
Drug Resistant Pneumonia Risk Factors		
Drug Resistant Organism Risk, n (%)	5,155 (5%)	1,504 (8%)
Hospitalization within past 90 days, n (%)	11,024 (11%)	2,780 (16%)
IV antibiotics within past 90 days, n (%)	7,314 (8%)	1,879 (11%)
Prior MRSA respiratory isolation, n (%)	910 (1%)	259 (1%)
Prior MRSA isolation any source, n (%)	2,649 (3%)	756 (4%)
Prior *P. aeruginosa* respiratory isolation, n (%)	1,237 (1%)	396 (2%)
Prior *P. aeruginosa* isolation any source, n (%)	2,862 (3%)	883 (5%)
Pneumonia Severity Factors		
PSI Risk Class, n (%)		
I – low risk of death	2,499 (3%)	149 (1%)
II	16,096 (17%)	1,392 (8%)
III	24,925 (26%)	2,868 (16%)
IV	42,641 (44%)	8,132 (45%)
V – high risk of death	10,998 (11%)	5,336 (30%)
PSI Risk Score, median (IQR)	93 (75 - 113)	112 (90 - 134)
Detection of Resistant Organisms by Culture		
MRSA, n (%)	1,714 (2%)	743 (4%)
P. aeruginosa, n (%)	1,897 (2%)	749 (4%)

Prior isolations included any positive culture within the VA system for a given patient within 1 year prior to the index hospitalization.
CAP = community acquired pneumonia. ICU = intensive care unit. IQR = interquartile range. MRSA = methicillin resistant *Staphylococcus aureus*. PSI = pneumonia severity index ADDIN CSL_CITATION {"citationItems":[{"id":"ITEM-1","itemData":{"DOI":"10.1056/NEJM199701233360402","ISSN":"0028-4793","PMID":"8995086","abstract":"BACKGROUND There is considerable variability in rates of hospitalization of patients with community-acquired pneumonia, in part

because of physicians' uncertainty in assessing the severity of illness at presentation. METHODS From our analysis of data on 14,199 adult inpatients with community-acquired pneumonia, we derived a prediction rule that stratifies patients into five classes with respect to the risk of death within 30 days. The rule was validated with 1991 data on 38,039 inpatients and with data on 2287 inpatients and outpatients in the Pneumonia Patient Outcomes Research Team (PORT) cohort study. The prediction rule assigns points based on age and the presence of coexisting disease, abnormal physical findings (such as a respiratory rate of > or = 30 or a temperature of > or = 40 degrees C), and abnormal laboratory findings (such as a pH <7.35, a blood urea nitrogen concentration > or = 30 mg per deciliter [11 mmol per liter] or a sodium concentration <130 mmol per liter) at presentation. RESULTS There were no significant differences in mortality in each of the five risk classes among the three cohorts. Mortality ranged from 0.1 to 0.4 percent for class I patients (P=0.22), from 0.6 to 0.7 percent for class II (P=0.67), and from 0.9 to 2.8 percent for class III (P=0.12). Among the 1575 patients in the three lowest risk classes in the Pneumonia PORT cohort, there were only seven deaths, of which only four were pneumonia-related. The risk class was significantly associated with the risk of subsequent hospitalization among those treated as outpatients and with the use of intensive care and the number of days in the hospital among inpatients. CONCLUSIONS The prediction rule we describe accurately identifies the patients with community-acquired pneumonia who are at low risk for death and other adverse outcomes. This prediction rule may help physicians make more rational decisions about hospitalization for patients with pneumonia.","author":[{"dropping-particle":"","family":"Fine","given":"M J","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Auble","given":"T E","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Yealy","given":"D M","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Hanusa","given":"B H","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Weissfeld","given":"L A","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Singer","given":"D E","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Coley","given":"C M","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Marrie","given":"T J","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Kapoor","given":"W N","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"The New England journal of medicine","id":"ITEM-1","issue":"4","issued":{"date-parts":[["1997","1","23"]]},"page":"243-50","title":"A prediction rule to identify low-risk patients with community-acquired pneumonia.","type":"article-journal","volume":"336"},"uris":["http://www.mendeley.com/documents/?uuid=60b6d68b-29d1-415e-acb4-5557903ac0c1"]}],"mendeley":{"formattedCitation":"[19]","plainTextFormattedCitation":"[19]"},"properties":{"noteIndex":0},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}[19].

Table 3. Performance characteristics of observed vs. guideline-expected empiric antibiotic selection against microbiological detection of MRSA and *P. aeruginosa* CAP

Comparison (95% CI)	*Sensitivity %*	*Specificity %*	*Diagnostic odds ratio*	*Under-coverage %*[b]	*Over-coverage %*[c]
Hospital Ward (N = 97,159)					
Anti-MRSA					
Observed	64 (62 – 66)	72 (72 – 73)	4.6 (4.3 – 4.9)	0.6 (0.6 – 0.7)	27.3 (27.0 – 27.6)
Guideline	10 (09 – 12)	99 (99 – 99)	14.7 (12.4 – 17.3)	1.6 (1.5 – 1.7)	0.8 (0.7 – 0.8)
Anti-PA					
Observed	52 (50 – 55)	73 (73 – 74)	3.0 (2.8 – 3.2)	0.9 (0.9 – 1.0)	26.2 (25.9 – 26.4)
Guideline	16 (15 – 18)	99 (99 – 99)	20.2 (17.7 – 22.9)	1.6 (1.6 – 1.7)	1.0 (0.9 – 1.0)
ICU (N = 17,877)					
Anti-MRSA					
Observed	87 (85 – 90)	42 (41 – 43)	5.0 (4.6 – 5.4)	0.5 (0.4 – 0.6)	55.5 (54.8 – 56.2)
Guideline[a]	21 (18 – 24)	92 (92 – 92)	3.1 (2.6 – 3.6)	3.3 (3.0 – 3.5)	7.7 (7.3 – 8.1)
Cx history	07 (05 – 09)	99 (99 – 99)	9.1 (6.4 – 13.0)	3.5 (3.3 – 3.8)	0.7 (0.6 – 0.9)
Exposure	13 (10 – 15)	93 (93 – 93)	1.9 (1.5 – 2.4)	3.3 (3.1 – 3.6)	6.8 (6.4 – 7.1)
Anti-PA					
Observed	80 (77 – 83)	46 (46 – 47)	3.5 (3.2 – 3.8)	0.8 (0.7 – 1.0)	51.4 (50.7 – 52.1)
Guideline[a]	30 (27 – 34)	92 (91 – 92)	4.7 (4.1 – 5.4)	2.9 (2.7 – 3.2)	8.1 (7.7 – 8.5)
Cx history	14 (11 – 17)	99 (99 – 99)	15.9 (12.2 – 20.8)	3.1 (2.9 – 3.4)	1.0 (0.8 – 1.1)
Exposure	13 (10 – 16)	93 (92 – 93)	1.9 (1.5 – 2.4)	3.0 (2.7 – 3.2)	6.9 (6.5 – 7.2)

[a] In severe CAP (in the ICU), guideline anti-MRSA or anti-PA therapy is recommended if the patient has previously had a positive respiratory culture for MRSA/PA in the past year (Cx history), or has been exposed to either a hospitalization or IV antibiotics within the past 90 days (exposure). Nested rows for Cx history and Exposure indicate performance of guideline-recommended antibiotic selection stratified by those indications.
[b] under-coverage % = 100 * (False negatives / N) = proportion of all hospitalizations in which MRSA/PA was detected but did not receive empiric anti-MRSA/anti-PA therapy.
[c] over-coverage % = 100 * (False positives / N) = proportion of all hospitalizations in which empiric anti-MRSA/anti-PA therapy was used but MRSA/PA was not detected.
CAP = community acquired pneumonia. CI = confidence interval. ICU = intensive care unit. MRSA = methicillin resistant *Staphylococcus aureus*. PA = *Pseudomonas aeruginosa.* Cx = culture.

FIGURES LABELS

Figure 1. Observed vs. guideline-expected culturing and empiric antibiotic selection practices

Each plot depicts the proportion of hospitalizations with the indicated practice. Markers connected by colored lines represent proportions at the facility level under observed (closed dots: •) and guideline-expected (open diamonds ◊) conditions. Adjacent boxplots depict the variability in these proportions, with median facility proportion labeled with text. For all observed-guideline proportion comparisons, $p<0.001$ by Cochran-Mantel-Haenszel tests with stratification by facility. MRSA = methicillin resistant *Staphylococcus aureus*. PA = *Pseudomonas aeruginosa*

Figure 2. Reclassification of observed vs. guideline-expected culturing and MRSA/*P. aeruginosa* (PA) case detection in hospital wards

Panels **(A)** and **(B)** show contingency 2x2 tables between observed and guideline-expected respiratory and blood culturing. Insets show respective results for observed sent cultures. Panels **(C)** and **(B)** show contingency 2x2 tables between observed and guideline-expected case detection of MRSA and *P. aeruginosa* by combined respiratory and blood culture results. Since observed-absent guideline-expected-present cultures are theoretical, the case detection from these is unknown and marked by "NA". Abbreviations: MRSA = methicillin resistant *Staphylococcus aureus*. PA = *Pseudomonas aeruginosa.*