Validation of a Clinical Score for Assessing the Risk of Resistant Pathogens in Patients With Pneumonia Presenting to the Emergency Department

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Background. Resistant organisms (ROs) are increasingly implicated in pneumonia in patients presenting to the emergency department (ED). The concept of healthcare-associated pneumonia (HCAP) exists to help identify patients infected with ROs but may be overly broad. We sought to validate a previously developed score for determining the risk for an RO and to compare it with the HCAP definition.

Methods. We evaluated adult patients admitted via the ED with bacterial pneumonia (January–December 2010). We defined methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas aeruginosa, and extended-spectrum β-lactamases as ROs. The risk score was as follows: 4, recent hospitalization; 3, nursing home; 2, chronic hemodialysis; 1, critically ill. We evaluated the screening value of the score and of HCAP by determining their areas under the receiver-operating characteristic (AUROC) curves for predicting ROs.

Results. The cohort included 977 patients, and ROs were isolated in 46.7%. The most common organisms included MRSA (22.7%), P. aeruginosa (19.1%), and Streptococcus pneumoniae (19.1%). The risk score was higher in those with an RO (median score, 4 vs 1; P < .001). The AUROC for HCAP equaled 0.62 (95% confidence interval [CI], .58–.65) versus 0.71 (95% CI, .66–.73) for the risk score. As a screening test for ROs, a score > 0 had a high negative predictive value (84.5%) and could lead to fewer patients unnecessarily receiving broad-spectrum antibiotics.

Conclusions. ROs are common in patients presenting to the ED with pneumonia. A simple clinical risk score performs moderately well at classifying patients regarding their risk for an RO.

Pneumonia represents a leading reason for admission to the hospital. Historically, pathogens such as Streptococcus pneumoniae, Haemophilus influenzae, and Legionella species have accounted for the main concerns in patients presenting to the emergency department (ED) with pneumonia [1]. More recently, physicians have increasingly isolated organisms usually implicated in nosocomial pneumonia among individuals coming to the hospital with lung infections [2–4]. This trend led to the creation of the concept of healthcare-associated pneumonia (HCAP) [5]. The purpose of HCAP was to help clinicians identify patients who, despite experiencing the onset of their pneumonia outside the hospital, are at risk for infections with highly resistant organisms (ROs) such as Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus (MRSA).

The presence of any 1 of several factors, including admission from a nursing home, recent hospitalization, prior antibiotic exposure, immunosuppression, and chronic hemodialysis (HD), defines HCAP and separates it from community-acquired pneumonia (CAP) per treatment guidelines [5]. Because of the high prevalence of these characteristics in patients...
who present to the hospital, many have expressed concern that antibiotic treatment decisions driven by the concept of HCAP might lead to excessive prescription and abuse of broad-spectrum anti-infectives [3, 4]. This, in turn, could lead to unnecessary costs and promote resistance. Supporting this concern are analyses suggesting that as many as 50% of persons presenting to the ED with pneumonia meet criteria for HCAP [3–5]. These studies similarly report that the incidence of ROs only ranges from 10% to 30% [3–5]. To address this limitation of the HCAP concept, investigators have developed multiple risk assessment models that refine the HCAP criteria [6, 7]. The dual goals of more precise clinical decision making and the containment of antibiotic misuse underscore the logic of these alternative scoring systems. Unfortunately, most of these risk-scoring approaches have never been validated outside the populations from which they were created [6, 7].

One further concern with reports correlating the presence of ROs with HCAP revolves around the actuality that prior studies describing the microbiology of HCAP have been significantly incomplete [2, 3, 7]. These investigations have often failed to use the entire definition of HCAP; rather, they applied a modified definition of HCAP because the researchers lacked data on some aspect of the HCAP definition, such as information regarding recent antibiotic exposure or hospitalization [2, 3, 7]. As such, these accounts of HCAP and its sensitivity and specificity as a screen for ROs may either overestimate or underestimate the concept’s true utility.

We sought to explore the screening properties of the complete HCAP definition in light of these limitations in earlier descriptions of the epidemiology and microbiology of HCAP, along with the lack of external validation of risk scores for identifying ROs. Concurrently, we aimed to assess the accuracy of a previously created risk assessment tool. We hypothesized that the risk-score approach would prove more accurate than the complete HCAP definition and, consequently, result in fewer patients potentially being given broad-spectrum antibiotic therapy unnecessarily.

**METHODS**

**Patients and Definitions**

We retrospectively evaluated adult (aged >18 years) patients admitted to a single hospital with pneumonia between January and December 2010. We restricted the analysis to patients with evidence of bacterial infection and initial presentation to the ED. We excluded patients transferred from other hospitals directly to the wards or the intensive care unit (ICU). This study was approved by the Washington University School of Medicine Human Studies Committee.

The presence of pneumonia necessitated both signs and symptoms of infection (ie, elevated white blood cell count or >10% band forms, fever, or hypothermia) along with a chest imaging study revealing an infiltrate(s). One investigator (M. H. K.), blinded to the determination of HCAP, reviewed the chest imaging. The diagnosis of a bacterial infection required a positive culture of either blood, pleural fluid, sputum, or the lower airways. We also considered a positive urinary antigen for either S. pneumoniae or Legionella as documentation of a bacterial infection.

**HCAP and Risk Score**

We employed a comprehensive definition of HCAP [5]. We considered HCAP present if the patient met any 1 of the following criteria: recent hospitalization for at least 48 hours during the preceding 90 days, admission from a long-term care (LTC) facility, receipt of HD or wound care, immunosuppression, and/or recent treatment (within the previous 30 days) with broad-spectrum antimicrobials. We defined patients as immunosuppressed if they had AIDS, active malignancy undergoing chemotherapy, and/or were treated with immunosuppressants (ie, 10 mg prednisone or equivalent daily for at least 30 days or alternate agents such as methotrexate).

The risk score we assessed has been previously described [6]. In brief, points were assigned as follows: 4 for recent hospitalization, 3 if presenting from a LTC facility, 2 if chronic HD, 1 if admitted to the ICU within 24 hours of evaluation in the ED, for a possible maximum score of 10. One investigator (A. F. S.) calculated the risk score blinded to, and independent from, the determination if the patient suffered from CAP versus HCAP. The current population for study is separate from the population from which the risk score was originally derived.

**Endpoints and Covariates**

The isolation of an RO served as our primary endpoint. Specifically, we examined the proportions of MRSA, P. aeruginosa, Acinetobacter baumannii, and extended-spectrum β-lactamase organisms as ROs and considered any of these to represent a pathogen of interest. In addition to demographic data (eg, age, gender, race) we compared patients infected with an RO to those with other organisms with respect to both the presence of HCAP relative to CAP and the calculated risk score. We further evaluated the individual aspects of the HCAP criteria and severity of illness. For severity of illness, we noted if the patient required admission to the ICU and if the patient underwent mechanical ventilation (MV).

The proportion of patients without ROs who would be classified as potentially needing broad-spectrum antibiotics (eg, defined as HCAP) represented a secondary endpoint. We assumed that the false-positive rates relating to classification as infection with an RO described patients who were likely to unnecessarily receive broad-spectrum antibiotic therapy.

**Statistics**

Univariate analyses were conducted with either the Fisher exact test or Student t-test as appropriate. Continuous,
nonparametrically distributed data were assessed with the Mann–Whitney U test. All analyses were 2 tailed, and a P value < .05 was assumed to represent statistical significance. We used traditional 2 × 2 tables to further calculate the sensitivity and specificity of the HCAP definition and a risk score, respectively, to classify patients for the presence of an actual infection with an RO.

We determined the area under the receiver-operating characteristic (AUROC) curves for both the HCAP definition and the risk score. We further calculated the 95% confidence intervals (CIs) surrounding calculations of the respective AUROCs. All analyses were conducted with SPSS software, version 17.0 (SPSS, an IBM Company).

RESULTS

The final cohort included 977 patients (mean [standard deviation] age, 60.5 [16.9] years, 55.7% male). The most common pathogens recovered were MRSA (22.7%), P. aeruginosa (19.1%), S. pneumoniae (19.1%), methicillin-sensitive S. aureus (14.1%), H. influenzae (8.0%), Klebsiella pneumoniae (5.6%), Escherichia coli (5.4%), and A. baumannii (4.8%). ROs were isolated in 46.7% of patients. Approximately three-quarters of the cohort met at least 1 criterion for HCAP.

Table 1 shows the characteristics of patients infected with ROs and those with pneumonia due to a non-RO pathogen. There were no differences in demographics between groups. Patients with ROs, however, were more severely ill and were nearly twice as likely to need ICU admission (odds ratio [OR], 2.04 [95% CI, 1.58–2.64]; P < .001) and MV (OR, 1.94 [95% CI, 1.50–2.50]; P < .001), respectively. Similarly, each of the HCAP criteria occurred more often in patients with ROs. For example, 25.4% of patients with ROs were admitted from LTC facilities compared with 11.1% of patients without infection due to an RO (P = .001). Overall, 91.0% of patients with ROs met the definition for HCAP. Nonetheless, 65.6% of patients with non-ROs were classified as HCAP. Emphasizing the prevalence of the various risk factors defining HCAP, patients infected with an RO met a median of 2 criteria for HCAP. Conversely, we observed a median of 1 HCAP criterion (P < .001) in those with a non-RO.

Figure 1 demonstrates the distribution of calculated risk scores relative to the prevalence of ROs. As the score increased, so did the probability of recovering from an RO. For example, among patients with a score of 0, the prevalence of ROs was approximately 15%, while nearly three-quarters of those with a score >6 were infected with ROs (P < .001). The median risk score in the cohort with an RO was 4 as opposed to 1 in the group with non-RO bacteria (P < .001).

Figure 2 reveals the receiver-operating characteristic (ROC) curves for the HCAP definition and for the risk score. As the ROC curves document, the risk score had higher sensitivity than the HCAP definition for nearly the entire range of specificities. Reflecting this, the AUROC was higher for the risk score. The AUROC for HCAP equaled 0.62 (95% CI, .58–.65) whereas the AUROC for the risk score was 15% higher (0.71 [95% CI, .66–.73]; P = .045 for the difference in AUROCs).

A comparison of screening characteristics of the HCAP definition and a risk score >0 for identifying persons infected with ROs is presented in Table 2. Overall, the risk score proved more accurate. Applying the HCAP definition as the trigger for initiating broad-spectrum antibiotics directed at ROs would result in 35.0% of the population being overtreated. In other words, the HCAP definition, as a surrogate for ROs, misidentified approximately one-third of all patients presenting to the ED with

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Resistant Organism (n = 456)</th>
<th>No Resistant Organism (n = 521)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>61.1 (16.2)</td>
<td>60.0 (17.5)</td>
<td>.321</td>
</tr>
<tr>
<td>Male</td>
<td>58.8%</td>
<td>53%</td>
<td>.081</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>57.9%</td>
<td>54.5%</td>
<td>.320</td>
</tr>
<tr>
<td>African-American</td>
<td>41.2%</td>
<td>44.7%</td>
<td>.478</td>
</tr>
<tr>
<td>Other</td>
<td>0.9%</td>
<td>0.8%</td>
<td>.828</td>
</tr>
<tr>
<td>Severity of illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU admission</td>
<td>62.5%</td>
<td>44.9%</td>
<td>.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>52.9%</td>
<td>36.7%</td>
<td>.001</td>
</tr>
<tr>
<td>HCAP risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTC admission</td>
<td>25.4%</td>
<td>11.1%</td>
<td>.001</td>
</tr>
<tr>
<td>HD</td>
<td>10.3%</td>
<td>4.8%</td>
<td>.001</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>37.1%</td>
<td>27.8%</td>
<td>.003</td>
</tr>
<tr>
<td>Prior antibiotics</td>
<td>58.6%</td>
<td>31.3%</td>
<td>.001</td>
</tr>
<tr>
<td>Recent hospitalization</td>
<td>55.9%</td>
<td>33.4%</td>
<td>.001</td>
</tr>
<tr>
<td>HCAP</td>
<td>91.0%</td>
<td>65.6%</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: HCAP, healthcare-associated pneumonia; HD, hemodialysis; ICU, intensive care unit; LTC, long-term care; SD, standard deviation.
pneumonia as having an RO, when in fact they were infected with a traditional CAP pathogen. Alternatively, utilizing a risk score \( >0 \) as the marker for empiric broad-spectrum antibiotics would result in only 24.3% of patients unnecessarily receiving anti-infectives for ROs. As a tradeoff, an additional 2.4% of patients (\( n = 5 \)) with an RO would receive initially inappropriate therapy not covering ROs.

DISCUSSION

This epidemiologic study of pneumonia patients presenting to the ED confirms that ROs often occur in this syndrome. Although organisms such as \( S. pneumoniae \) remain prevalent, bacteria historically isolated in nosocomial pneumonia now arise in many patients initially evaluated in the ED. Additionally, the majority of patients meet the definition for HCAP. Despite this, HCAP has poor specificity as a screening test for ROs. As a corollary, application of the HCAP concept to guide antibiotic treatment potentially leads to a large proportion of patients unnecessarily receiving broad-spectrum regimens. On the other hand, a simple risk score both appears valid for assessing the probability of an RO in patients initially hospitalized via the ED and is more accurate than the HCAP definition. Utilization of the risk score could potentially lead to the unnecessary initial use of broad-spectrum agents.

Prior studies have documented the increasing prevalence of ROs in pneumonia present at admission. For example, Kollef et al noted that MRSA accounted for 14% of the pathogens isolated in a retrospective, multicenter analysis of hospitalized pneumonia patients [2]. Micek et al confirmed this observation and further reported that resistant gram-negative bacteria, such as \( P. aeruginosa \), occurred with moderate frequency in the ED [3]. Specifically, 18% of all pneumonias were determined to be caused by \( P. aeruginosa \). Similarly, in an evaluation of patients who presented to the ED with pneumonia necessitating MV, Schreiber et al noted ROs in approximately one-third of their cohort [7]. Descriptions of the microbiology of pneumonia in the ED from both Europe and Asia have reported similar shifts in the distribution of pathogens causing these infections [4, 8, 9]. Our results are consistent with these earlier evaluations. However, it now appears that ROs have increased in prevalence and are now as frequent as more traditional CAP pathogens.

It was initially hoped that the concept of HCAP would foster just such risk stratification. Unfortunately, it appears that HCAP, as a concept, does not adequately address this concern. Although ROs clearly occur more often in HCAP than in CAP, utilization of HCAP as a screening test for ROs leads to substantial misclassification. In turn, many patients whose infections are not due to an RO may receive overly broad antibiotic regimens. As the current study demonstrates, nearly one-third of patients with pneumonia in the ED would unnecessarily receive broad-spectrum treatment if the HCAP criteria were employed to guide antibiotic decision making. Given the prevalence of HCAP generally, along with this high rate of misclassification, use of HCAP routinely in treatment algorithms will likely lead to needless cost. Of greater concern, administering unneeded anti-infectives violates a key principle of antibiotic stewardship. Such behavior promotes both resistance and \( Clostridium difficile \) infection [10]. In light of the already escalating rates of antimicrobial resistance, physicians must strive to avoid approaches that may accelerate this trend. Future treatment guidelines must acknowledge and address these inadequacies with the HCAP definition and balance the need to emphasize achieving initially appropriate therapy against concerns about encouraging further antimicrobial abuse. While HCAP has served as a useful notion to encourage clinicians to recognize the prevalence of resistant infections in the ED, it now appears prudent to modify the approach to pneumonia patients presenting to the hospital. If clinicians fail to grasp the implications of overuse of broad-spectrum agents

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**Table 2. Screening Characteristics of Healthcare-Associated Pneumonia Versus Risk Score**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCAP definition</td>
<td>91.0%</td>
<td>34.3%</td>
<td>54.8%</td>
<td>81.3%</td>
<td>60.7%</td>
</tr>
<tr>
<td>Risk score ( &gt;0 )</td>
<td>88.6%</td>
<td>54.5%</td>
<td>63.0%</td>
<td>84.5%</td>
<td>70.4%</td>
</tr>
</tbody>
</table>

Abbreviations: HCAP, healthcare-associated pneumonia; NPV, negative predictive value; PPV, positive predictive value.
and do not embrace approaches that limit this problem, future clinicians will face even more difficult challenges in the care of these patients.

Clinical risk scoring to assess the potential for ROs may represent an improvement over an HCAP-based approach. Our findings are novel, therefore, in that few risk assessment scoring systems for use in the ED are validated in datasets other than the ones from which they were derived. That our risk score more accurately categorizes patients as to the potential for an RO in a second, separate population suggests the robustness of the model. Others have proposed different risk-scoring approaches, but those specific risk models for identifying ROs have been limited [7]. They either were created on very circumscribed populations (eg, ICU patients) or were never externally validated [7]. Despite these issues, however, a risk-scoring approach seems to consistently surpass the HCAP definition. More important, as we show, adoption of the present risk score leads to fewer patients unnecessarily receiving broad-spectrum agents, because a low absolute score results in a high negative predictive value.

Why does our risk score outperform the HCAP definition? First, the HCAP definition weights each of its individual components equally [5]. It appears that select risk factors (eg, chronic HD) are not as important as others. Second, the current concept of HCAP fails to integrate issues related to severity of illness. ROs appear more frequently in critically ill patients on a consistent basis [2, 3, 7]. This may be due to the fact that ROs are either inherently more virulent or because such ROs arise in patients who, for some reason, seek medical care later in the course of their illnesses.

Although the current risk model has enhanced accuracy, it represents only a modest improvement over the HCAP definition alone. The score still miscategorizes 30% of patients. This drawback of our clinical score suggests that factors other than those included in it contribute to the risk of ROs. Our findings, thus, suggest that a multicenter epidemiology study is needed to help create a risk assessment model that has both higher sensitivity and specificity. Alternatively, the present results emphasize the need for the development of rapid diagnostic tools that allow clinicians to know quickly and reliably if their patient is suffering from pneumonia due to an RO. Moreover, the tools must be designed to have high specificity because clinical criteria are sufficiently sensitive. In the future, some combination of a risk score that objectively estimates the pretest probability for an RO along with a biomarker that provides more objective evidence of the presence of an RO will be required—a situation akin to the present approach to pulmonary embolism. Some form of sequential testing may prove even more effective. As a first step, either the risk score or HCAP definition could be applied, given their high sensitivities. Subsequently, a second risk tool, which would have a high specificity and be designed to identify ROs in the remaining population, would be employed.

Despite our large sample size, the current study has several significant limitations. First, we restricted our analysis to patients with evidence of bacterial infection. Current diagnostic and culture methods may be imprecise. We likely missed patients whose cultures were falsely negative. Conversely, a positive culture may only reflect colonization rather than true infection. Second, sputum cultures may not necessarily reflect the pathogen actually causing the pneumonia, given the potential discordance between what one recovers from the sputum as opposed to the organism that might have been found through lower-airway evaluation. In that same vein, viral pathogens may cause pneumonia. Given this possibility and the reality that some patients with acute viral infections will meet criteria for HCAP, we may have underestimated the proportion of patients who are over-treated with the HCAP rubric. Unfortunately, each of these is a concern with nearly every study of the microbiology of pneumonia in nonventilated patients. Third, notwithstanding our endeavor to evaluate all aspects of the HCAP definition, we likely falsely categorized some patients based on a lack of information regarding recent antibiotic exposure. Medical records, especially when reviewed retrospectively, do not necessarily note this. Also, patients may not recall if they were recently treated with such agents. Fourth, our data originate from 1 institution. Hence, our findings may not apply to other institutions, as the generalizability of the results is limited.

In conclusion, ROs commonly cause pneumonia in patients presenting to the hospital. However, the notion of HCAP, as currently envisioned, lacks precision. Application of the HCAP concept possibly results in the administration of broad-spectrum antibiotics to many patients not requiring them. A clinical risk score that reflects a modification of the HCAP definition appears valid and surpasses the HCAP approach with respect to overall accuracy. It may also help limit antibiotic overuse.

Notes

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Potential conflicts of interest. A. F. S. has served as a consultant to or speaker for or has received grant support from Astellas, Bayer, Forrest, Pfizer, Theravance, and Trius. M. D. Z. has served as a consultant to or has received grant support from Astellas, Forrest, J and J, and Pfizer. M. H. K. has served as a consultant to or speaker for or has received grant support from Cubist, Hospria, Merck, and Sage. S. T. M. has received grant support from Cubist, Optimer, Merck, and Pfizer. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


