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Original Research

CRITICAL CARE MEDICINE

Resistant Pathogens in Nonnosocomial Pneumonia and Respiratory Failure

Is It Time To Refine the Definition of Health-care-Associated Pneumonia?

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Background: **The concept of health-care-associated pneumonia (HCAP) exists to identify patients infected with highly resistant pathogens. It is unclear how precise this concept is and how well it performs as a screening tool for resistance.**

Methods: **We retrospectively identified patients presenting to the hospital with pneumonia complicated by respiratory failure. We examined the microbiology of these infections based on pneumonia type and determined the sensitivity and specificity of HCAP as a screen for resistance. Through logistic regression and modeling, we created a scoring tool for determining who may be infected with resistant pathogens.**

Results: **The cohort included 190 subjects (37% with ARDS) and we noted resistant pathogens in 33%. Resistance was more common in HCAP (78% vs 44%, $P = .001$). HCAP alone performed poorly as a screening test (sensitivity and specificity 78.3% and 56.2%, respectively). Variables independently associated with a resistant organism included immunosuppression (adjusted odds ratio [AOR] 4.85, $P < .001$), long-term care admission (AOR 2.36, $P = .029$), and prior antibiotics (AOR 2.12, $P = .099$). A decision rule based only on these factors performed moderately well at identifying resistant infections. The presence of HCAP itself, based on meeting defined criteria, was not independently associated with resistance using logistic regression to control for covariates.**

Conclusions: **HCAP is common in patients presenting to the hospital with pneumonia leading to respiratory failure. The HCAP concept does not correlate well with the presence of infection due to a resistant pathogen. A simpler clinical decision rule based on select HCAP criteria performs as well as the HCAP concept for potentially guiding antibiotic decision making.**

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Abbreviations: AOR = adjusted odds ratio; AUROC = area under the receiver operating curve; CAP = community-acquired pneumonia; ESBL = extended-spectrum β-lactamase; HCAP = health-care-associated pneumonia; HD = hemodialysis; LTC = long-term care; MRSA = methicillin-resistant *Staphylococcus aureus*; MV = mechanical ventilation; PA = *Pseudomonas aeruginosa*

Pneumonia remains a leading reason for admission to the hospital. Historically, patients presenting to the hospital with pneumonia were thought to be at risk for pathogens such as *Streptococcus pneumoniae* and *Legionella* spp.[1] These bacteria were considered discrete from those responsible for nosocomial infections (eg, methicillin-resistant *Staphylococcus aureus* [MRSA] and *Pseudomonas aeruginosa* [PA]). However, emerging data have led many to question this distinction between community-acquired and hospital-acquired processes. Studies document that patients now present to the hospital with infections caused by MRSA and other highly resistant bacteria.[2,3] To address this concern and to better characterize the shifting microbiology, the concept of health-care-associated pneumonia (HCAP) was created.[4] HCAP describes cases in whom the onset of pneumonia occurs outside the hospital but, nonetheless, the patient has an ongoing interaction with the health-care system. Specifically, HCAP is defined as pneumonia in a patient presenting to the hospital who has been recently hospitalized, comes from long-term

care (LTC), requires chronic hemodialysis (HD) or wound care, has been treated with antibiotics recently, and/or is immunosuppressed.[4]

HCAP may account for >50% of pneumonias admitted to the hospital.[3] HCAP also appears to identify patients at high risk for poor outcomes, particularly because they seem likely to receive initially inappropriate therapy. Although the HCAP concept may facilitate identification of patients at high risk for infection with a resistant pathogen and, in turn, promote higher rates of initially appropriate therapy, there are little data validating the ability of the current definition of HCAP to accomplish this.[5] One concern associated with the evolution of HCAP as a unique syndrome is that its adoption may lead to greater use of broad-spectrum agents when they may not be needed. In other words, if HCAP does not provide sufficient resolution to separate persons with highly resistant pathogens from those with traditional pathogens, physicians may prescribe antimicrobials that are unnecessary, which can augment costs and promote resistance.

We hypothesized that the HCAP definition would identify persons somewhat more likely to be infected with a resistant pathogen. However, we further theorized that the HCAP concept would perform poorly at segregating those with traditionally nosocomial pathogens from those with historically community-acquired bacteria, particularly in critically ill subjects. To evaluate our hypothesis, we conducted a retrospective analysis of all patients who presented to our hospital with respiratory failure due to pneumonia and focused on the microbiology of these infections.

Materials and Methods

Subjects and Definitions

We included adult (aged >18 years) patients admitted with respiratory failure requiring mechanical ventilation (MV) for pneumonia between January 2004 through December 2007. We required that patients needed MV within 24 h of admission. We restricted the analysis to people with evidence of bacterial infection. We excluded patients transferred from other hospitals directly to the wards or the ICU. There were no other exclusions.

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The presence of pneumonia required signs and symptoms of infection (ie, elevated WBC count or >10% band forms, fever or hypothermia, and so forth), along with a compatible chest image revealing infiltrate(s). All images were reviewed by one investigator blinded as to the determination of HCAP. The presence of a bacterial infection required a positive culture of either blood, pleural fluid, or lower-airway secretions. We also considered a positive urine antigen for either *Streptococcus pneumonia* or *Legionella* as evidence of a bacterial process. At our institution, all MV patients with suspected pneumonia undergo invasive testing with blind bronchial bush on a routine, protocolized basis. A sputum culture alone was not considered evidence of bacterial infection. Our institution is an urban, tertiary care center with 900 beds, including a medical ICU containing 19 beds.

HCAP

We considered HCAP present when at least one of the following criteria was met: recent hospitalization (last 90 days), admission from an LTC facility, chronic HD or wound care, immunosuppression, and/or recent treatment (last 30 days) with broad-spectrum antimicrobials. We defined as immunosuppressed those persons with AIDS, active malignancy undergoing chemotherapy, and/or those undergoing treatment with immunosuppressants (ie, 10 mg prednisone or equivalent daily for at least 30 days or alternate agents such as methotrexate). Broad-spectrum antimicrobials included extended-spectrum (ie, coverage against PA) β-lactams, monobactams, carbepenems, and cephalosporins. We also included anti-MRSA agents such as linezolid, vancomycin, and tigecycline as broad-spectrum antibiotics.

End Points and Covariates

The presence of a resistant pathogen served as our primary end point. Specifically, we examined rates of MRSA, PA, and extended-spectrum β-lactamase (ESBL) organisms and considered any of these to represent a pathogen of interest. In addition to comparing demographic information, we compared patients with a resistant pathogen to those with other organisms with respect to the presence or absence of HCAP, severity of illness, and comorbid illnesses. Severity of illness was measured by the Acute Physiology and Chronic Health Evaluation II score, the need for vasopressors, and the Pao_2/Fio_2 ratio at presentation.[6] Comorbid illnesses of interest included hypertension, congestive heart failure, coronary artery disease, diabetes mellitus, COPD, and malignancy.

Statistics

Univariate analyses were conducted with either the Fisher exact test or Student *t* test as appropriate. All analyses were two tailed, and $P < .05$ was assumed to represent statistical significance. We further calculated the sensitivity and specificity of the HCAP definition at identifying patients with a resistant organism.

We relied on logistic regression to identify independent factors associated with the presence of an infection due to MRSA, PA, or an ESBL as a pooled end point. Variables significant at the $P < .20$ level, along with factors we felt *a priori* to be associated with a resistant infection, were entered into the model. Variables were assessed for colinearity and the model's goodness of fit was evaluated with the Hosmer-Lemeshow C-statistic.

Based on the logistic regression, we created a point scoring tool to determine a subject's risk of pneumonia with a highly resistant pathogen. The adjusted odds ratios (AORs) from the logistic regression were converted into points based on the β coefficients, and a total point score was determined for each patient. The ability of the score to correlate with resistant infection was measured

based on its area under the receiver operating curve (AUROC) as a screening test.

Results

The final cohort included 190 subjects (mean age 60.9 ± 15.9 years, 54.2% men). Resistant pathogens were noted in 32.6% (n = 60) of subjects. Specifically, MRSA, PA, and ESBL were recovered in 18.4%, 13.2%, and 1.0% of subjects, respectively. Conversely, we diagnosed *S pneumoniae*, MRSA, and *Legionella* in 14.2%, 12.6%, and 2.6% of patients, respectively. Table 1 shows the pathogen distribution based on pneumonia type.

As Table 2 shows, there was no difference in either demographics or severity of illness between persons with infection due to a resistant organism and those with a traditionally susceptible isolate. There also was no difference in the prevalence of comorbid illnesses across the two cohorts. More patients with a resistant pathogen met the definition for HCAP (78.3% vs 43.8%, $P = .001$). However, not every component of the HCAP definition contributed equally to this distinction. The prevalence of HD and of recent hospitalization was similar in those with and without an infection due to MRSA, PA, or an ESBL. In addition, some patients (n = 17) with community-acquired pneumonia (CAP) nonetheless had infection with a resistant pathogen. The most common of these pathogens was MRSA, accounting for 14 of these 17 occurrences. As Figure 1 reveals, the probability of infection with a resistant bacterium increased as the patient met more criteria for HCAP. In addition (Fig 1), persons who met at least two criteria for HCAP were nearly four times more likely to have a resistant pathogen identified, compared with a patient fulfilling fewer than two components of the HCAP definition. Overall, HCAP alone performed poorly as a screening test for pneumonia due to a resistant organism. The sensitivity and specificity were 78.3% and 56.2%, respectively, although the positive and negative predictive values equaled 45.2% and 84.9%, respectively. Based on the receiver operating curve for HCAP as a screening test for resistant infection, the AUROC was 0.67.

Table 1—*Pathogens by Pneumonia Type*

Pathogen	HCAP (n = 94)	CAP (n = 96)	*P* Value
Resistant organisms			
MRSA	22.3	14.6	.193
PA	23.4	3.1	.001
ESBL-producing organisms	2.1	0.0	.001
Nonresistant organisms			
Streptococcus pneumoniae	6.4	21.9	.003
Streptococcus viridans	10.6	29.2	.002
Methicillin-susceptible	10.6	14.6	.514
Staphylococcus aureus			
Escherichia coli	12.8	4.2	.038
Klebsiella pneumoniae	10.6	4.2	.102
Legionella species	3.2	2.1	.681

Data are given as percentages. CAP = community-acquired pneumonia; ESBL = extended-spectrum β-lactamase; HCAP = health-care-associated pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus;* PA = *Pseudomonas aeruginosa*.

Logistic regression analysis revealed several variables independently associated with recovery of a resistant organism. Immunosuppressed patients were nearly five times more likely to be infected with MRSA, PA, or an ESBL (AOR, 4.85; 95% CI, 2.22-10.61; $P < .001$). Recovery of a resistant pathogen was also independently associated with admission from LTC (AOR, 2.36; 95% CI, 1.09-5.10; $P = .029$). The relationship between prior antibiotic exposure and a history of COPD approached statistical significance. Overall, the model had a good fit, as indicated by the C-statistic ($P = .711$). Of note, the presence of HCAP itself, based on meeting any of the criteria defined previously, was not associated with resistant infection. In a second logistic regression where meeting more than two HCAP criteria was entered into the model in place of HCAP, this correlated with pneumonia due to one of the pathogens of interest (AOR, 2.53; 95% CI, 1.21-5.33; $P < .014$). Immunosuppression, additionally, and beyond its inclusion as a factor potentially leading to meeting two or more HCAP criteria, remained linked with the presence of a resistant pathogen (AOR, 2.98; 95% CI, 1.27-7.03; $P = .012$). As with the initial logistic regression model, a history of COPD trended toward being an independent predictor of MRSA, PA, or an ESBL (AOR, 2.00; 95% CI, 0.91-4.41; $P = .084$). This second model also had a good fit (C-statistic $P = .511$).

Based on the results of these models, we developed a clinical scoring tool to identify persons with a resistant pathogen. Patients received points as follows: immunosuppression, 3; admission from LTC, 2; and prior antibiotics, 1; this lead to a maximum possible score of 6. Figure 2 displays the prevalence of resistant organisms as a function of the total point score. As the score increases, the frequency of infection due to MRSA, *P aeruginosa*, and ESBLs increases. In patients with two or more points, there was a > 40% chance of a resistant pathogen. As a screening test, the score had an AUROC of 0.71. If one dichotomizes the proposed score as < 2 vs ≥ 2, then the sensitivity and specificity are 80.5% and 63.3%, respectively. However, even among patients with none of these potential factors, some still were infected with resistant organisms. Specifically, 15 of 86 patients (17.4%) with none of the above "risk factors" had infection with a resistant organism.

Table 2—*Baseline Characteristics*

	Resistant Organism (n = 60)	No Resistant Organism (n = 130)	*P* Value
Demographics			
Age, y	59.5 ± 15.2	61.5 ± 16.2	.425
Male	58.3	52.3	.531
Race, %			
White	10.0	13.8	.478
Black	83.3	70.0	
Other	6.7	16.2	
Severity of illness			
APACHE II score	29.0 ± 8.0	28.0 ± 8.5	.482
Glasgow Coma Score	6.8 ± 2.8	6.4 ± 2.9	.352
Pao_2/Fio_2	266.3 ± 162.6	256.0 ± 179.5	.704
ARDS	37.3	37.5	.999
Vasopressors	48.3	42.6	.530
Comorbid illnesses			
Hypertension	38.3	50.8	.120
Diabetes mellitus	25.0	28.5	.727
Coronary artery disease	23.2	19.2	.564
Congestive heart failure	23.3	19.2	.564
COPD	26.7	17.7	.178
Malignancy	23.3	14.6	.153
HCAP risk factors			
LTC admission	43.3	19.2	.001
HD	21.7	12.3	.128
Immunosuppression	38.3	12.3	.001
Prior antibiotics	28.3	11.5	.006
Recent hospitalization	28.3	19.2	.160
HCAP	78.3	43.8	.001

Data are given as mean ± SD or percentages. APACHE = Acute Physiology and Chronic Health Evaluation; HD = hemodialysis; LTC = long-term care. See Table 1 for expansion of other abbreviations.

Discussion

This retrospective analysis of patients presenting to the hospital with pneumonia complicated by respiratory failure necessitating MV indicates that HCAP is common in the ICU. Moreover, many of these patients are infected with pathogens traditionally implicated in nosocomial infections. The presence of these pathogens is elevated in persons with HCAP. However, the currently envisioned definition of HCAP performs marginally at segregating those with infection due to MRSA, PA, and ESBLs from persons infected with traditional CAP organisms. Additionally, severity of illness does not seem to distinguish between pathogen types, and each of the HCAP criteria does not seem to contribute equally to explaining the burden of resistant organisms.

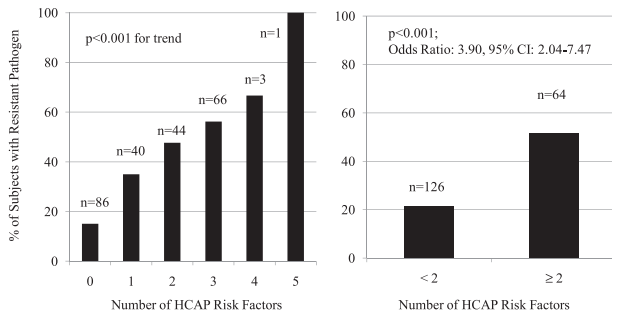

Figure 1. Prevalence of resistant pathogens as a function of HCAP risk factors. HCAP = health-care-associated pneumonia.

Prior analyses document that HCAP appears to represent a distinct syndrome.[2,3,7-9] In a review of a large, administrative database, Kollef and colleagues[2] found that the microbiology of HCAP was distinct from that of CAP. In addition, they found that HCAP represented nearly one-third of all admissions for pneumonia.[2] In a single-center review of patients presenting to the ED with pneumonia, Micek and colleagues[3] confirmed that the microbiology of HCAP differed from that of CAP and that patients with HCAP were more likely to be infected with a resistant pathogen, to receive inappropriate antibiotic therapy, and to die. They also estimated that more than one-half of pneumonias admitted via the ED could be classified as HCAP. International reports from Japan and Italy reveal that HCAP, as defined by the current American Thoracic Society/Infectious Disease Society of America position statement on nosocomial pneumonia, captures a cohort of patients more likely infected with MRSA, PA, and ESBLs.[7,8] Each of these earlier reports, however, has been limited. First, they have often relied on administrative data, as opposed to patient-level data, which exposes them to various forms of bias.[2] Second, they have either not reported culture data, as with the study from Italy, or they have failed to focus on the critically ill, a naturally more homogenous group of individuals relative to all patients admitted to the hospital.[7]

Our survey builds on these earlier reports. First, we demonstrated that potentially resistant pathogens are now commonly encountered in critically ill patients coming to the hospital with pneumonia. Second, our results underscore that the HCAP concept does highlight a group of patients at increased risk of infection with organisms traditionally confined to the hospital. Third, HCAP as currently conceived nonetheless may be inadequate for capturing the burden of resistant organisms. After controlling for multiple confounders, we did not find that meeting the definition for HCAP, of and within itself, was independently associated with the presence of infection with the bacteria of interest. Beyond that, HCAP performed poorly as a screening test for pneumonia caused by MRSA, PA, or ESBLs. Furthermore, no other reports have examined how each of the component pieces of the HCAP definition contributes to explaining (if at all) the prevalence of resistant pathogens in critically ill individuals with nonnosocomial pneumonia. For example, that chronic HD did not correlate with recovery of a resistant pathogen suggests

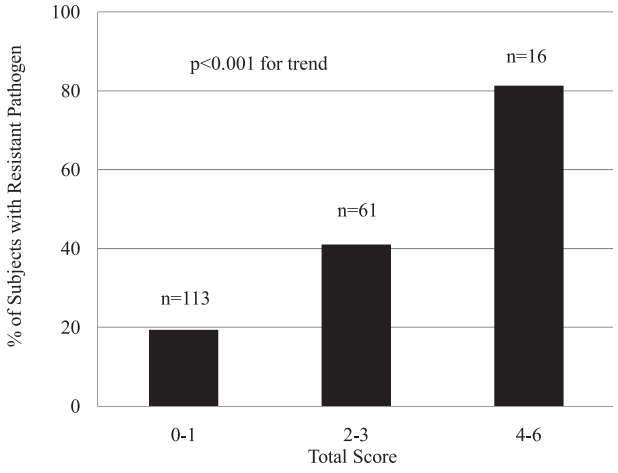

FIGURE 2. Prevalence of resistant pathogens as a function of risk scores. Distribution of resistant pathogens as a function assigned risk points based on the two risk scoring systems. The score points are assigned as follows: immunosuppression, 3; admission from long-term care, 2; and prior antibiotics, 1; leading to a maximum possible score of 6.

that it may be prudent to reexamine the proposed definition of HCAP.

Only one earlier study has described a clinical risk stratification tool to refine the HCAP concept in order to allow the clinician to more precisely determine which patients are at high risk of infection with organisms necessitating broad-spectrum antibiotic therapy.[5] That study identified four independent variables associated with resistant infection and proposed a scoring tool similar to ours. Although this earlier study included patients with a range in severity of illness, the authors documented that the HCAP definition alone misclassifies many patients. Taken together, their results and ours suggest that development of a more precise risk-stratification tool is possible and that HCAP alone may be too blunt a concept for widespread use. In other words, simply reserving broad-spectrum initial therapy to patients with "HCAP" may lead to undertreatment of some subjects, and the attendant risks of inappropriate therapy. Alternatively, adoption of HCAP as a unique classification could lead to overuse of antibiotics in other cases. We believe prospective epidemiologic studies directly comparing HCAP and various risk scores are urgently needed. Our clinical decision tool, moreover, highlights that one can develop a more restrictive risk-stratification approach while maintaining overall accuracy. In other words, although our risk score performed as well as the overall HCAP definition, it was able to achieve this with a narrower focus on select HCAP risk factors.

Our analysis has several important limitations. Its retrospective nature underscores that our observations are prone to multiple forms of bias. We attempted to limit the impact of this by ensuring that all cases were reviewed to make sure that radiologic studies clearly indicated that the patient had pneumonia. The single-center design, along with the focus on persons with respiratory failure, necessarily limits the generalizability of our findings. As such, physicians must explore their local data to determine if our results are applicable in their settings. Beyond that, our findings may not apply to persons not requiring ICU care. Nonetheless, our data indicate that we ought not to presume that with the evolution of HCAP, we have adequately addressed concerns about the spread of traditionally nosocomial pathogens beyond the hospital. We also analyzed only patients with culture evidence of infection. Cultures may be negative in patients even though they have a bacterial infection. However, given our emphasis on microbiology, it was necessary to limit the population to these individuals. Alternatively, in MV patients, tracheal aspirates may not reflect the true culprit pathogen. Hence, one strength of our design is that we essentially relied on lower airway cultures. Finally, our study may have been underpowered to detect some differences where they existed. With a larger sample size, we might have been able to determine that some factors that were not independently related to resistant infection (eg, renal disease, recent hospitalization) would, in fact, be associated with it.

CONCLUSIONS

In sum, persons presenting to the hospital with severe pneumonia and respiratory failure are at high risk of infection with pathogens traditionally thought to be confined to nosocomial infections. Those with HCAP are more likely to be infected with MRSA, PA, and ESBLs. The presence of HCAP alone does not reliably indicate that a patient is infected with such an organism. Patients without CAP needing MV may also be infected with such pathogens. Clinical scoring tools may either simplify or make more precise the process of identifying critically ill patients with nonnosocomial pneumonia in need of broad-spectrum initial therapy.

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