Healthcare-associated pneumonia: Who is truly at risk for multidrug-resistant pathogens?

MICHELLE PEAHOTA, BHAVIK M. SHAH, CLAUDINE EL-BEYROUTY, AND JASON J. SCHAFER

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In 2005, joint guidelines issued by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) provided the first definition of healthcare-associated pneumonia (HCAP). This new classification was added to the existing classes of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) and represented a significant change in pneumonia management. The change was particularly important with regard to patients acquiring pneumonia in a community setting. The guidelines recognized that a changing healthcare delivery system meant that patient exposures to healthcare environments and healthcare-associated pathogens no longer occurred exclusively in acute care settings but could occur in a growing spectrum of community healthcare settings such as skilled nursing centers, long-term care facilities, infusion centers, and dialysis clinics. With a growing potential for such exposures, it was recognized that patients with pneumonia traditionally diagnosed and managed as CAP may instead have healthcare-related pathogen exposures and infections requiring treatment more consistent with that provided for HAP.

To help clinicians identify patients presenting with pneumonia in community settings whose pneumonia may be caused by healthcare-associated pathogens, the guidelines specifically defined HCAP as pneumonia occurring in any patient who has had a recent (i.e., within 90 days) acute care hospitalization lasting longer than 2 days, has resided in a nursing home or long-term care facility, has attended a hospital or hemodialysis clinic, or has received i.v. antibiotic therapy, chemotherapy, or wound care in the past 30 days. For management, the guidelines stated that all patients with HCAP should receive treatment targeted to multidrug-resistant (MDR) pathogens, as is routinely recommended for the treatment of HAP.

While the intent of developing the HCAP category—to help guide empirical therapy in patients who meet the specified criteria—can be justified in principle, there are limitations to both the ATS–IDSA definition of HCAP and the recommendations for HCAP management that continue to require resolution. For example, the criteria used to define HCAP were not derived from pneumonia-specific studies but were instead extrapolated from a single-center, prospective, observational study of healthcare-associated bloodstream infections. As a result, concerns have been raised that the risk factors listed in the definition of HCAP may not be entirely accurate. The most appropriate criteria for identifying patients with HCAP remain unclear.

It also remains unclear whether treatment with broad-spectrum antibiotics targeted against MDR pathogens is necessary for all patients with HCAP. Patients with HCAP are heterogeneous, with differences in their contact with the healthcare system, their comorbid conditions, their geographic locations, and many other factors that influence the risk of exposure to MDR pathogens. Given the potential variability in the level of risk for MDR pathogen exposure among these patients, a more detailed assessment of risk is necessary to improve antibiotic

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decision-making. Furthermore, the use of the ATS–IDSA definition of HCAP in clinical practice has increased the use of broad-spectrum antibiotics in patients admitted to a hospital for pneumonia. Concerns about adverse events and antibiotic resistance have been raised; perhaps more importantly, data have emerged regarding possible risks of administering broad-spectrum therapy to all patients with HCAP. At least one study showed a greater risk of mortality in patients with HCAP risk factors who received guideline-concordant broad-spectrum therapy relative to patients treated for CAP.

After the publication of the ATS–IDSA guidelines, several investigations designed to address questions related to the HCAP definition were performed. These questions included the following: What is the etiology of HCAP? How does treatment based on the HCAP definition affect outcomes? Do the criteria specified in the HCAP definition accurately predict infection with MDR pathogens? Are there proposed alternative methods of predicting which patients harbor MDR pathogens? This article will attempt to answer these questions by reviewing pertinent literature and providing a particular focus on emerging research evaluating new strategies for identifying and managing patients with HCAP, including those likely exposed to MDR pathogens. It will also identify areas of continuing need for research to determine the proper strategy for HCAP management in the future.

What is the etiology of HCAP?

The presumed etiology of HCAP was extrapolated from data on patients with ventilator-associated pneumonia (VAP), and, as a result, the ATS–IDSA treatment recommendations for HCAP and HAP were as well. Therefore, the question arises as to whether the etiology of pneumonia in patients with HCAP is truly similar to the etiology of HAP and VAP or more consistent with CAP etiology. Several studies have attempted to answer this question. However, the results have varied according to geography and the definitions of HCAP used in each study.

Five studies have evaluated the etiology of HCAP in patients from the United States. In the largest study, by Kollef et al., data on 4543 patients admitted to 59 hospitals with CAP, HCAP, HAP, or VAP from January 2002 through December 2003 were retrospectively evaluated. Of these patients, 988 were classified as having HCAP based on the following criteria: transfer from another healthcare facility, receipt of long-term hemodialysis, and prior hospitalization within 30 days. Staphylococcus aureus was more commonly identified in patients with HCAP, HAP, or VAP than in those with CAP. Methicillin-resistant S. aureus (MRSA) was identified significantly more often in the HCAP group (18.3%) than in either the CAP (6.2%) or the VAP (11.8%) group, but the frequency of MRSA detection did not differ significantly from that in the HAP group (16.8%). The occurrence of Pseudomonas aeruginosa was significantly higher in the HCAP group (25.3%), as compared with the CAP (17.1%) and HAP (18.4%) groups, but did not differ significantly from the rate of occurrence in the VAP group (21.2%). Overall, this study supported the assertion that resistant pathogens are more common in patients classified as having HCAP than in patients presenting with CAP. However, it is important to note that the definition of HCAP used by Kollef et al. was not identical to that found in the ATS–IDSA guidelines, and risk factors such as receipt of i.v. antibiotics, chemotherapy, and wound care within 30 days were not considered in this study. Moreover, it was not specified whether patients transferred from another healthcare facility included those coming from a nursing home or long-term care facility.

Three single-center retrospective reviews evaluated the etiology of pneumonia in patients with HCAP. In a study of 639 patients hospitalized with pneumonia during the period 2003–05, four variables were associated with the presence of resistant organisms: prior hospitalization within 90 days, nursing home residence, need for long-term hemodialysis, and need for intensive care unit (ICU) admission. The investigators noted that the presence of resistant organisms did not completely correlate with the fulfillment of the HCAP criteria. Overall rates of isolation of resistant organisms, including MRSA and P. aeruginosa, were high (45.2%). The definition of HCAP used in this study included patients with underlying immunosuppression but did not include those receiving outpatient i.v. antibiotics, chemotherapy, or wound care. In a related study of the same cohort of patients admitted with pneumonia (n = 639), the researchers compared rates of MDR pathogens between patients with CAP and HCAP. Rates of identification of MRSA, P. aeruginosa, non-lactose-fermenting gram-negative bacilli, and Enterobacteriaceae were higher in the HCAP group than in the CAP group (30.6% versus 12.0% for MRSA, 25.5% versus 4.8% for P. aeruginosa, 10.0% versus 1.9% for non-lactose-fermenting gram-negative bacilli, and 9.0% versus 2.4% for Enterobacteriaceae). Streptococcus pneumoniae, Haemophilus influenzae, and Legionella species were more commonly identified in patients with CAP versus HCAP. This study also included immunocompromise in the definition of HCAP but did not include wound care and included i.v. therapy only if administered at a hospital clinic. In a secondary review of data on a subset of 396 patients with
HCAP from the aforementioned study of Micek et al.10 (the same definition of HCAP was used in the follow-up study), MRSA, P. aeruginosa, and gram-negative bacilli were again found to be the most commonly isolated pathogens.11

While three of the four studies summarized above included nursing home residence in the definition of HCAP,9-11 a separate study evaluated CAP versus nursing home–acquired pneumonia (NHAP) in 104 patients 75 years of age or older who were admitted to an ICU with a diagnosis of pneumonia during the period 1996–99.12 A microbiological etiology was identified in 53% of these patients. S. pneumoniae and Legionella species were the most commonly identified organisms in the patients with CAP (14% and 9%, respectively), while S. aureus (predominantly methicillin-susceptible S. aureus) was more common in the NHAP group than in the CAP group (29% of patients versus 7% of patients). Notably, rates of isolation of gram-negative bacilli were similar in the two groups.

Taken together, these five studies indicated that there is a difference in the microbiological etiology of pneumonia in patients labeled as having HCAP or NHAP as opposed to CAP. In each study, isolation of MRSA, P. aeruginosa, or gram-negative bacilli (or a combination thereof) was more common in patients with some risk factors for nosocomial infection. However, in each study the definition of HCAP differed from the ATS–IDSA definition. Most importantly, three of the four studies involving patients with HCAP included immunosuppression as a risk factor, while the ATS–IDSA guidelines acknowledge that immunosuppression increases the risk of infection with MDR organisms but do not include it in the definition of HCAP. The majority of these studies did not include the receipt of i.v. antibiotics, chemotherapy, or wound care within the prior 30 days in the definition of HCAP, while the ATS–IDSA guidelines do. While nursing home patients were included in three of the four studies of HCAP etiology, only one study specifically identified residence in a nursing home as an independent risk factor for infection with resistant organisms.8 It can be concluded that in the United States, recent hospitalization, attendance at a hospital clinic, nursing home or long-term care facility residence, the need for long-term hemodialysis, and immunosuppression increase the risk of infection with nosocomial pathogens. The current U.S. data do not support the remaining criteria for HCAP used in the ATS–IDSA guidelines.

Our literature search identified five European and two Asian studies that evaluated the etiology of HCAP.13-19 The definition of HCAP used in five of the studies13,14,17-19 was identical to that specified in the ATS–IDSA guidelines. Two of the seven published studies specifically investigated NHAP15,16; both excluded immunocompromise from the definition of HCAP, unlike the majority of pertinent U.S. studies. In contrast to the U.S. studies, all of the non-U.S. studies evaluated found that S. pneumoniae was the most commonly identified organism in both CAP and HCAP. Three studies found that rates of infection with resistant organisms such as MRSA and gram-negative bacilli were higher in patients with HCAP but much lower overall than those found in the U.S. studies.13,17,19 In contrast to the U.S. study comparing the etiologies of CAP and NHAP,12 which found that S. aureus was more common in patients with NHAP, a European study of these two groups found only one case of S. aureus in either group, while S. pneumoniae was the predominant pathogen in both groups.35

Overall, the studies performed outside the United States using a definition of HCAP comparable to that found in the ATS–IDSA guidelines demonstrated lower rates of isolation of resistant organisms than the U.S. studies; this was likely due to a combination of geographic differences in resistance as well as the exclusion of immunocompromised patients. Three of the studies suggested that despite their low overall isolation rates, resistant organisms are isolated at increased rates in patients with HCAP.

Does treatment based on the HCAP definition affect outcomes?

The ATS–IDSA guidelines recommend using broad-spectrum antimicrobial therapy to cover MDR pathogens in all patients meeting the criteria for HCAP; however, there are limited data indicating that this practice improves patient outcomes. In a population-based cohort study, 15,071 cases of HCAP in non–critically ill patients were reviewed with the aim of identifying independent risk factors for mortality.8 Of the patients included in the review, 8.0% received guideline-recommended HCAP therapy, 75.7% received guideline-recommended CAP therapy, and 16.3% received therapy not concordant with either HCAP or CAP treatment guidelines. The baseline characteristics of patients treated with HCAP- and CAP-targeted regimens were similar; however, patients who were treated with a regimen for HCAP were more likely to have been hospitalized within the previous 90 days and to have multiple HCAP risk factors. An adjusted multivariate analysis showed that recent hospital admission and receipt of HCAP-targeted therapy were independent risk factors for 30-day mortality. In their report on the study findings, the investigators expressed their belief that HCAP-targeted therapy was not likely responsible for the increase in mortality and that confounding variables not captured by the study methodology, such as severity of disease, might have contributed to the results.
A recent study by Chen et al. sought to evaluate clinical outcomes in patients with HCAP who were initially treated with HCAP or CAP guideline–concordant antimicrobial therapy (i.e., broad-spectrum and narrower-spectrum antibiotics, respectively). The study included 228 HCAP admissions to a general medical ward at a Veterans Affairs medical center; all patients met the criteria for HCAP according to the ATS–IDSA guidelines. Patients admitted from a long-term care facility, those who required direct ICU admission, and those with nosocomial pneumonia were excluded from the study. Regimens considered to constitute HCAP-targeted therapy included one or more agents with activity against *P. aeruginosa*. Patients who received other regimens were assigned to the CAP therapy group. The primary outcome was the rate of clinical cure at 30 days after hospital discharge. Secondary endpoints included hospital length of stay, the rate of readmission within 90 days of discharge, 30-day postdischarge mortality, duration of i.v. antibiotic use, and microbiological response.

During the 228 inpatient admissions evaluated by Chen and colleagues, 106 patients received HCAP therapy and 122 received CAP therapy. Patient demographics were similar between the two groups, including mean Pneumonia Severity Index (PSI) scores. Hospitalization within 90 days of admission was the most common reason patients were classified as having HCAP. The primary endpoints, 30-day postdischarge treatment-attributable and overall clinical cure rates, were similar between the CAP therapy group and the HCAP therapy group (75.4% versus 69.8% [*p* = 0.34] and 59.8% versus 54.7% [*p* = 0.44], respectively. Patients treated with HCAP regimens had significantly longer lengths of stay and durations of i.v. antimicrobial therapy. There was no difference in the overall readmission rate, but there was an increased rate of readmissions specifically due to pneumonia in the HCAP therapy group relative to the CAP therapy group (15.1% versus 6.56%, *p* = 0.035). Patients prescribed regimens for CAP required antibiotic escalation more frequently than patients prescribed regimens for HCAP due to inadequate initial response (14.8% and 6.6%, respectively, *p* = 0.045), but the antimicrobials used during therapy escalation were not reported. Pathogen eradication rates and mortality were similar between the two groups.

There were several limitations to the study of Chen et al. Since it had a retrospective design, there was a lack of randomization and control over interventions. Given that 84.6% of patients met the criteria for HCAP because they had been hospitalized within the 90 days prior to admission, there was little representation of other HCAP-qualifying criteria, such as recent home i.v. therapy, wound care, or recent receipt of hemodialysis; therefore, the study results may not be generalizable to the entire population of patients who would be categorized as having HCAP according to the ATS–IDSA guidelines. Lastly, only about one quarter of the patients had positive culture results, making it difficult to draw meaningful conclusions regarding microbiological eradication.

The ATS–IDSA guidelines provide HCAP criteria to identify patients presenting with pneumonia in community healthcare settings who likely harbor MDR pathogens, and broad-spectrum therapy is recommended for these patients. However, in the study performed by Chen et al., there was no difference in the clinical cure rates between those who received broad-spectrum versus narrow-spectrum antimicrobial therapy. This finding suggests that perhaps not all patients who meet HCAP criteria require treatment targeting MDR pathogens.

Do the ATS–IDSA criteria for HCAP accurately predict infection with MDR pathogens?

A comprehensive meta-analysis that evaluated the rates of isolation of MDR organisms in patients with HCAP and patients with CAP and quantified the predictive ability of the HCAP criteria was recently published. The meta-analysis included 24 studies involving a total of 22,456 patients. All studies were published from 2005 (after the ATS–IDSA guidelines were published) to 2013. Less than half the studies (*n* = 9, 37.5%) were prospective. Asia was the most common study location (*n* = 12, 50%), followed by Europe (*n* = 9, 37.5%) and North America (*n* = 3, 12.5%). Only 5 studies used the ATS–IDSA definition of HCAP. Inclusion of immunosuppressed patients was the most commonly cited reason for the use of a modified definition of HCAP (*n* = 15, 62.5%). The primary outcome was the comparative frequencies of potentially MDR organisms in HCAP and CAP.

Relative to patients with CAP, patients with HCAP were at increased risk for infection with MRSA (odds ratio [OR], 4.72; 95% confidence interval [CI], 3.69–6.04), *P. aeruginosa* (OR, 2.75; 95% CI, 2.04–3.72), or Enterobacteriaceae (OR, 2.11; 95% CI, 1.69–2.63). The risk of infection with potentially MDR organisms did not differ significantly in the Asian, European, and North American studies, which contrasts with previous findings discussed above; this finding should be interpreted cautiously, as it may have been due to the low number of evaluated studies conducted in North America (*n* = 3, 12.5%). There was, however, statistically significant publication bias for MDR organisms. Additionally, patients with HCAP were more likely to have microbiological testing (OR, 1.23; 95% CI, 1.07–1.41) and positive results (OR, 1.35; 95% CI, 1.15–1.59). Together, these limitations may confound and thus exaggerate...
the microbiological differences between HCAP and CAP.

The definition of HCAP was not found to be a reliable tool for identifying patients at risk for infection with potentially MDR organisms. The definition was found to have low sensitivity (53.7%; 95% CI, 52.2–55.2%) and specificity (71.2%; 95% CI, 70.5–71.9%). Similarly, the HCAP definition was not an effective tool for discriminating individual resistant pathogens, including MRSA (sensitivity, 69.0% [95% CI, 65.9–72.0%]; specificity, 65.7% [95% CI, 65.0–66.4%]), *P. aeruginosa* (sensitivity, 52.2% [95% CI, 49.2–55.1%]; specificity, 67.7% [95% CI, 67.1–68.4%]), and Enterobacteriaceae (sensitivity, 42.9% [95% CI, 41.0–44.8%]; specificity, 66.1% [95% CI 65.5–66.8%]). The researchers also measured the predictive ability of the HCAP definition through determination of the area under the summary receiver operator characteristic curve (AUROCC) by calculating pooled positive and negative likelihood ratios; an AUROCC of ≥0.75 was defined as the threshold for clinical usefulness. The HCAP definition performed poorly in prospective (AUROCC, 0.64; 95% CI, 0.62–0.66) and high-quality (AUROCC, 0.66; 95% CI, 0.62–0.70) studies; the calculated values indicated better performance in North American (0.74; 95% CI, 0.68–0.80) and Asian (0.72; 95% CI, 0.70–0.75) studies but were below the specified threshold for clinical utility. The authors estimated that the number needed to treat (NNT) for an HCAP regimen versus a CAP regimen (i.e., the number of patients who would have to be treated with broad- versus narrower-spectrum antibiotics in order to benefit 1 patient in terms of appropriate coverage of an MDR pathogen) as 4–499 for MRSA, 5–330 for *P. aeruginosa*, and 6–282 for Enterobacteriaceae; these wide ranges of NNT values are related to the variable underlying prevalences of MDR pathogens in the respective studies. The high calculated NNT values call into question the 2005 ATS–IDSA guidelines’ recommendation of broad-spectrum antibiotics for all patients with HCAP.

The available data suggest that the set of HCAP criteria identified in the ATS–IDSA guidelines may not be a reliable tool for predicting the presence of MDR pathogens and that broad-spectrum antibiotics are not warranted in all patients meeting these criteria. The reported rates of MDR organism–associated HCAP in these studies were affected by several factors, including the most common modification to the criteria (the inclusion of immunosuppressed patients), disparate rates of microbiological testing and positive results between patients with CAP and HCAP, and publication bias, as well as geographic differences in resistance patterns. Consideration should be given to local resistance patterns to determine the necessity for routine broad-spectrum antibiotic use.

What are the proposed alternative methods of predicting which patients with HCAP likely harbor MDR pathogens?

Since the HCAP definition does not adequately differentiate patients with pneumonia who are and who are not at risk for infection with MDR pathogens, several scoring tools have been proposed to help guide empirical antibiotic selection.

Shorr et al.’s previously discussed retrospective observational analysis of 639 patients with sputum or lower airway culture–positive HCAP sought to identify differential risk factors for HCAP caused by resistant organisms. In that study, four independent variables were identified as risk factors for HCAP caused by resistant organisms: hospitalization within the past 90 days (adjusted OR [AOR], 4.21; 95% CI, 2.89–6.15), nursing home residence (AOR, 2.75; 95% CI, 1.74–4.33), long-term dialysis (AOR, 2.11; 95% CI, 1.03–4.31), and ICU admission (AOR, 1.62; 95% CI, 1.14–2.28). The investigators proposed the following scoring system: 4 points for recent hospitalization, 3 points for nursing home residence, 2 points for long-term dialysis, and 1 point for ICU admission. Patients with 6 or more points had a significantly higher risk of infection caused by a resistant organism than patients with either 3–5 points or 0–2 points (75%, 55%, and <20%, respectively; *p < 0.05*).

A similar scoring system was identified in a prospective observational European cohort study of 935 patients presenting with HCAP in community settings. Hospitalization within the previous 90 days (OR, 4.87; 95% CI, 1.90–12.4) and nursing home residence (OR, 3.55; 95% CI, 1.12–11.24) were identified as independent risk factors for infection with a resistant organism after adjustment for sex, age, and comorbidities. These risk factors were also associated with a significantly increased risk of inhospital mortality after adjustment for age, PSI score, infection severity, presence of severe sepsis, and appropriateness of antibiotic therapy. The investigators proposed a scoring system that accounts for patient comorbidities and exposure to a healthcare setting, with scores ranging from 0 (no risk factors) to 12.5 (all four risk factors present). Patients with scores of 3.0–12.5 points were at significantly higher risk for infection with a resistant pathogen relative to patients with scores of <0.5 point (38% versus 8%, *p < 0.001*).

A prospective study was undertaken to compare the predictive ability of the scoring systems developed by Shorr et al. (the Shorr score) and Aliberti et al. (the Aliberti score), as well as the HCAP criteria defined by the ATS–IDSA guidelines. A total of 3474 consecutive patients presenting with HCAP in community settings were enrolled at two European centers: one in Barcelona, Spain (*n* =
1591), and the other in Edinburgh, Scotland (n = 1883). Patients with immunosuppression, a history of solid organ transplantation, hospitalization within the preceding 14 days, or thoracic malignancy were excluded. The two scoring systems had higher predictive ability than the HCAP criteria, as measured by AUROC analysis. For the Barcelona sample, AUROC values for the Aliberti score (0.89; 95% CI, 0.83–0.95) and the Shorr score (0.89; 95% CI, 0.82–0.96) were higher than the value for the HCAP criteria (0.77; 95% CI, 0.69–0.83). Similar findings were reported in the Edinburgh cohort, with the Aliberti scoring system yielding the highest AUROC (0.77; 95% CI, 0.71–0.84), followed by the Shorr score (0.75; 95% CI, 0.68–0.81) and the HCAP criteria (0.66; 95% CI, 0.59–0.73). Compared with the Shorr score and HCAP criteria specified in the ATS–IDSA guidelines, the Aliberti scoring system yielded a higher AUROC for patients admitted to the ICU in both cohorts. Limitations of this study included the low prevalence of MDR organisms (7.6% in the Barcelona cohort and 3.3% in the Edinburgh cohort) relative to the U.S. prevalence and the exclusion of patients with immunosuppression. Nonetheless, the data suggested that the scoring tools may be more effective than the HCAP criteria in stratifying patients based on risk to guide empirical antibiotic selection.

Shindo and colleagues proposed a scoring system based on the results of a prospective observational multicenter study in Japan. The objective of the study was to identify risk factors associated with drug-resistant pathogens in patients hospitalized with either CAP or HCAP. The study included 1413 patients (526 with HCAP). Pathogens resistant to CAP-targeted drugs (i.e., ceftriaxone, ampicillin–sulbactam, macrolides, and respiratory fluoroquinolones) were identified at a significantly higher rate in the HCAP group (26.6% versus 8.6%, p < 0.001). However, the risk factors for drug-resistant pathogens were similar between the two cohorts. Six independent risk factors for the presence of drug-resistant pathogens were identified: hospitalization within the previous 90 days (AOR, 2.06; 95% CI, 1.23–3.43), immunosuppression (AOR, 2.31; 95% CI, 1.05–5.11), previous antibiotic use (AOR, 2.45; 95% CI, 1.51–3.98), gastric acid suppression (AOR, 2.22; 95% CI, 1.39–3.57), tube feeding (AOR, 2.43; 95% CI, 1.18–5.00), and nonambulatory status (AOR, 2.45; 95% CI, 1.40–4.30). The probability of identifying a pathogen resistant to CAP-targeted drugs increased with the addition of each risk factor, ranging from 3.5% in patients with no risk factors to 83.3% in patients with six risk factors. The authors proposed a scoring system involving simply counting the number of risk factors present. They suggested that patients with three or more risk factors be treated with broad-spectrum antibiotics and that patients with no or one risk factor be treated with a narrower-spectrum, CAP-targeted regimen. The predictive ability of this scoring tool was significantly higher (AUROC, 0.79; 95% CI, 0.74–0.84) than that of the system proposed by Aliberti et al. (AUROC, 0.66; 95% CI, 0.61–0.71) and nonsignificantly higher than that of the Shorr score (AUROC, 0.71; 95% CI, 0.66–0.77).

A prospective study sought to evaluate the need to prescribe antimicrobials with activity against MDR pathogens for patients with HCAP based on a scoring system that evaluated severity of illness and risk factors for infection with an MDR pathogen. Maruyama et al. performed a multicenter cohort study at six Japanese hospitals, evaluating 445 hospitalized patients with radiographic and clinical findings consistent with either CAP or HCAP. Patients considered to have HAP, those with pulmonary tuberculosis, and those with infiltrates not attributable to pneumonia were excluded from the study. For treatment of HCAP, the therapeutic strategy proposed by Brito and Niederman, which accounts for severity of illness and MDR pathogen risk factors (Table 1), was used. For purposes of the study, severe illness was defined as the need for mechanical ventilation or ICU admission. MDR pathogen risk factors included immunosuppression, hospitalization within the previous 90 days, poor functional status, and receipt of antimicrobials within six months. Study groups 1 and 2 consisted of patients with HCAP who were not considered to have severe pneumonia, and groups 3 and 4 consisted of patients with HCAP who had severe pneumonia. Patients with HCAP were prescribed antibiotics according to MDR pathogen risk level: patients in risk factor (groups 1 and 3) received CAP therapy, while those with two or more risk factors received HAP therapy.

The study of Maruyama et al. included 124 patients with CAP (28% of the study population) and 321 with HCAP. Relative to patients with CAP, patients with HCAP had significantly more MDR pathogen risk factors (mean ± S.D., 1.8 ± 1.3 versus 0.2 ± 0.4; p < 0.001). The most commonly isolated pathogen in both groups was S. pneumoniae. Overall, patients with HCAP had significantly higher rates of infection with S. aureus, MRSA, P. aeruginosa, and MDR pathogens. Although rates of S. aureus, MRSA, P. aeruginosa, and MDR pathogen infection were higher in the HCAP group overall, patients with no or only one MDR pathogen risk factor had significantly lower rates of infection with these pathogens relative to patients with two or more risk factors. The 30-day mortality rate was significantly lower in patients with CAP than in patients with HCAP (5.6% versus 13.7%, p =
Mortality was significantly higher in patients with HCAP who had two or more MDR risk factors than in those with no or one risk factor (18.2% versus 8.6%, \( p = 0.012 \)), which was not significantly different from the mortality of patients with CAP (5.6%, \( p = 0.346 \)). Regardless of MDR pathogen risk factors, severely ill patients with HCAP had a higher 30-day mortality rate than patients without severe illness. The rate of inappropriate initial therapy, defined as a regimen that did not have activity against an isolated pathogen, was low in the CAP and HCAP groups overall (3.1% and 7.1%, respectively). Despite receiving a CAP-targeted regimen, patients with HCAP with no or only one MDR pathogen risk factor had a low rate of initial inappropriate therapy (3.2%), which was similar to the rate in patients with CAP receiving CAP-targeted therapy (3.1%). Patients with HCAP who had two or more risk factors and were prescribed HCAP-targeted therapy received inappropriate therapy in 10.1% of cases.

In their multivariate analysis, Maruyama and colleagues found that nutritional status, PSI score, and initial treatment failure were independent predictors of 30-day mortality. Unlike treatment failure, inappropriate therapy was not predictive of 30-day mortality. Overall, the rate of treatment failure was higher than the rate of inappropriate therapy (19.6% and 7.1%, respectively), suggesting that treatment failure may have been attributable to patient-specific factors and not to inappropriate therapy.

The study of Maruyama et al. supported the theory that not all patients with HCAP require treatment with broad-spectrum antimicrobial therapy. It is interesting to note that patients with HCAP who had no or only one MDR pathogen risk factor received CAP-targeted therapy, and there was no difference in the rate of inappropriate therapy in those patients and patients with CAP. There were some notable study limitations. All of the study sites were located in Japan; as discussed previously, the etiology of pneumonia may not be similar in different areas of the world. Additionally, the rates of MRSA pneumonia were relatively low in both the CAP and HCAP groups (0% and 6.9%, respectively).

The aforementioned scoring tools may help clinicians decide which patients are at risk for MDR pathogens and require broad-spectrum antimicrobial therapy. Among other limitations, the scoring tools of Aliberti et al., Shorr et al., and Shindo et al. have not been evaluated in a prospective study aimed at determining their utility with regard to clinical outcomes in patients with HCAP. As discussed, the scoring tool proposed by Brito and Niederman has been evaluated in a prospective study. This scoring tool is based on disease severity in addition to the number of risk factors for the presence of drug-resistant pathogens. However, none of these scoring tools have been validated or applied in North America, where drug resistance patterns are considerably different from those in Asia or Europe. Nonetheless, the HCAP criteria specified in the ATS–IDSA guidelines do not reliably differentiate patients at risk for drug-resistant pathogens as a guide to empirical antibiotic selection. Although there are not enough data to identify the best scoring tool for that purpose, these strategies may have a role in identifying patients with HCAP who can be adequately treated with a narrow-spectrum regimen.

**Conclusion**

The current ATS–IDSA definition of HCAP is not consistently reliable for predicting which patients with pneumonia are infected with MDR pathogens. Use of the definition may lead to wrong empirical antimicrobial choices, and concerns have been raised regarding the need to use antimicrobials active against MDR pathogens in all patients with HCAP. Widespread use of broad-spectrum antimicrobial therapy may increase adverse events associated with antimicrobial use, including an increased risk of *Clostridium difficile*.

### Table 1. Risk Stratification and Treatment Algorithm for Healthcare-Associated Pneumonia

<table>
<thead>
<tr>
<th>No. Risk Factors for Multidrug-Resistant Pathogens</th>
<th>Group and Regimen</th>
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<tbody>
<tr>
<td><strong>Severe Pneumonia Not Present</strong></td>
<td></td>
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<tr>
<td>0 or 1</td>
<td>Group 1: quinolone monotherapy or ( \beta )-lactam + macrolide</td>
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<tr>
<td>( \geq 2 )</td>
<td>Group 2: antipseudomonal ( \beta )-lactam + antipseudomonal quinolone or aminoglycoside + optional vancomycin or linezolid</td>
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<tr>
<td><strong>Severe Pneumonia Present</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Group 3: ( \beta )-lactam + macrolide or quinolone</td>
</tr>
<tr>
<td>( \geq 1 )</td>
<td>Group 4: antipseudomonal ( \beta )-lactam + antipseudomonal quinolone or aminoglycoside + optional vancomycin or linezolid</td>
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\(^{a}\)Risk factors: hospitalization within previous 90 days, immunosuppression, poor functional status, and receipt of antimicrobials within 6 months.

\(^{b}\)Severe pneumonia defined as need for mechanical ventilation or admission to an intensive care unit.
infections and increased bacterial resistance. Receipt of HCAP-targeted therapy has been associated with increased hospital length of stay and a longer duration of i.v. antibiotic therapy, with no significant difference in clinical outcomes. Although therapy, with no significant difference in clinical outcomes.20 Although the ATS–IDSA definition of HCAP seeks to improve empirical therapy in patients whose pneumonia is likely due to healthcare exposures, it does not accurately predict infection with MDR pathogens; thus, its use may lead to unnecessary antimicrobial use and possible harm.5,8,20 Scoring tools to more accurately identify patients with HCAP likely to harbor MDR pathogens have been developed, but they have not been validated.4,6,9,19,21

The ATS–IDSA guidelines on management of HAP, VAP, and HCAP are currently under revision and are projected to be published by fall 2015. Hopefully, several limitations of the HCAP definition will be addressed and there will be additional guidance regarding selection of antimicrobial therapy. Will the guidelines incorporate scoring tools, based on patient risk factors and severity of illness, to identify patients with HCAP who may be infected with MDR pathogens? We anticipate that the revised ATS–IDSA guidelines will recommend MDR pathogen risk stratification and incorporation of local resistance patterns into decisions regarding individualized empirical treatment so that broad-spectrum antimicrobial therapy is judiciously prescribed.

References