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Guideline-Concordant Therapy and Outcomes in Healthcare-Associated Pneumonia

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Abstract

Healthcare-associated pneumonia (HCAP) guidelines were first proposed in 2005 but have not yet been validated. The objective of this study was to compare 30-day mortality in HCAP patients treated with either guideline-concordant HCAP (GC-HCAP) therapy or guideline-concordant community-acquired pneumonia (GC-CAP) therapy.

We performed a population-based cohort study of >150 hospitals in the U.S. Veterans Health Administration. Patients were included if they had ≥1 HCAP risk factor and received antibiotic therapy within 48 hours of admission. Critically-ill patients were excluded. Independent risk factors for 30-day mortality were determined in a generalized linear mixed-effect model, with admitting hospital as a random effect. Propensity scores for the probability to receive GC-HCAP therapy were calculated and incorporated into a second logistic regression model.

A total of 15,071 patients met study criteria and received GC-HCAP therapy (8.0%), GC-CAP therapy (75.7%), or non-guideline-concordant therapy (16.3%). The strongest predictors of 30-day mortality were recent hospital admission (OR 2.49, 95% CI 2.12-2.94) and GC-HCAP therapy (2.18, 1.86-2.55). GC-HCAP therapy remained an independent risk factor for 30-day mortality (OR 2.12, 95% CI 1.82-2.48) in the propensity score analysis.

In non-severe HCAP patients, GC-HCAP therapy is not associated with improved survival compared to GC-CAP therapy.

Keywords: pneumonia, guidelines for management of pneumonia, health outcomes, drug resistance

Introduction

In 2005, the American Thoracic Society and the Infectious Diseases Society of America introduced healthcare-associated pneumonia (HCAP) as a new pneumonia classification for patients admitted from the community who have had recent contact with the healthcare system [1]. The presence of an HCAP risk factor at admission (recent hospitalization, admission from a nursing home/long-term care facility, chronic dialysis, outpatient infusion therapy, home wound care, or family member with a multidrug-resistant [MDR] pathogen) indicates a potential higher risk for an MDR pathogen, and guidelines recommend that HCAP patients receive empiric antibiotic therapy similar to patients with hospital-acquired or ventilator-associated pneumonia.

The HCAP population has been characterized by several recent studies. These data indicate that HCAP patients are older, present with more severe disease, and suffer worse health outcomes than community-acquired pneumonia (CAP) patients [2-6]. Additionally, regional data from the United States (U.S.) suggest higher frequencies of MDR pathogens (specifically *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* [MRSA]) in HCAP patients [2, 4]. Although MDR pathogens may be more common in some HCAP cohorts, there are still a significant amount of traditional CAP pathogens isolated in HCAP patients, making HCAP criteria a relatively poor tool for predicting patients with MDR pathogens [7, 8]. The balance between adequate coverage and overtreatment is difficult, leading to controversy and confusion toward the best approach to caring for these patients.

If treating HCAP patients with guideline-concordant HCAP (GC-HCAP) antibiotics demonstrates improved mortality over HCAP patients treated with guideline-concordant CAP (GC-CAP) antibiotics, then the HCAP guidelines are effective and should remain the standard of treatment for HCAP patients. Under this premise, the following study aimed to validate HCAP

guidelines by comparing health outcomes in HCAP patients treated with GC-HCAP or GC-CAP therapy.

The primary objective of this study was to compare the effects of GC-HCAP therapy, GC-CAP therapy, and non-guideline-concordant (non-GC) therapy on patient mortality and hospital length of stay (LOS) in a cohort of hospitalized, non-critically-ill HCAP patients. The secondary objective was to describe differences in patient mortality and selected bacterial pathogens based on the number of HCAP risk factors present in each patient.

Methods

Administrative data from the U.S. Veterans Health Administration (VHA) was used to examine pneumonia care and mortality among patients with HCAP. The VHA databases are repositories of clinical data from more than 150 VHA hospitals and 850 VHA clinics. The Institutional Review Board of The University of Texas Health Science Center at San Antonio and the South Texas Veterans Health Care System Research and Development committee approved this study.

Patient Eligibility

All patients were required to have an *International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM)* principal discharge diagnosis of pneumonia (*ICD-9-CM* codes 480.0-483.99 or 485-487) in fiscal years 2002 to 2007 and at least one documented risk factor for HCAP. HCAP risk factors were defined as hospital admission in the previous 90 days, residence in a nursing home in the previous 90 days, receipt of outpatient intravenous antibiotics in the past 90 days, and hemodialysis. Patients undergoing hemodialysis were

identified using *ICD-9-CM* codes (table 1 of online supplementary material). Other HCAP risk factors were obtained from patient records maintained in VHA databases.

Patients were excluded if they were critically-ill or did not receive antibiotic therapy within 48 hours of hospital admission. Critically-ill patients were excluded to minimize differences in level of care between the groups, as critically ill patients suffer increased morbidity and mortality compared to those managed on general medical wards [9]. Patients not receiving antibiotics within 48 hours were excluded to reduce potential cases of hospital-acquired pneumonia. Critical illness was identified by: 1) admission to the intensive care unit (ICU) at any time during hospitalization; 2) the presence of *ICD-9-CM* codes indicating respiratory organ failure, cardiovascular organ failure, or invasive mechanical ventilation; or 3) the receipt of any vasopressor or inotrope. Vasopressors and inotropes included dobutamine, dopamine, epinephrine, isoproterenol, metaraminol, norepinephrine, and vasopressin.

BASELINE CHARACTERISTICS

Baseline demographics were recorded at the time of admission and comorbid illnesses were determined using *ICD-9-CM* codes from outpatient and inpatient care in accordance with the Charlson co-morbidity scoring system [10, 11]. Patient race was recorded for white and black patients, and ethnicity was reported for patients identifying themselves as Hispanic. Native Americans, Hawaiians, and patient records missing racial information were reported as "other." Tobacco use was defined as patients with a diagnosis of nicotine dependence, a recorded visit to a VHA tobacco cessation clinic, a current procedural terminology (CPT) treatment code for smoking (99406, 99407), or an outpatient prescription for a smoking cessation product (Zyban®, varenicline, Nicotrol®, nicotine replacement). *ICD-9-CM* codes were used to identify patients

with alcohol abuse/dependence and organ failure [12-14]. Medication use in the 90 days prior to admission was documented for cardiovascular medications, antidiabetic medications, inhaled corticosteroids, systemic corticosteroids (oral and/or injectable), and pulmonary medications (table 2 of online supplementary material).

Antibiotic Therapy and Bacterial Pathogens

Antibiotic therapy received within the first 48 hours of admission was evaluated using established consensus guidelines (table 1) [1, 15]. Patients receiving additional antibiotics beyond the minimum required to satisfy GC-HCAP or GC-CAP therapy remained in their respective treatment groups. The subset of patients who received both GC-HCAP and GC-CAP therapy was considered to have received GC-HCAP therapy. Patients receiving antibiotics that were not concordant with either CAP or HCAP guidelines were considered to have received non-GC therapy.

Pneumonia pathogens were identified using *ICD-9-CM* discharge diagnosis codes. Proportions of pneumonia due to *Streptococcus pneumoniae, S. aureus*, and *Pseudomonas* were compared by the number of HCAP criteria per patient. *Streptococcus pneumoniae* was selected because it is the most common pathogen in CAP and is generally susceptible to guideline-recommended CAP regimens. *Staphylococcus aureus* and *Pseudomonas* were selected because, in patients without specific risk factors, guideline-recommended CAP therapy has inadequate activity toward methicillin-resistant strains of *S. aureus* and all *Pseudomonas* [15]. *ICD-9-CM* codes used during the study period do not differentiate between methicillin-sensitive and methicillin-resistant *S. aureus*; therefore, all *S. aureus* species were included in our analyses.

While not reflected in all HCAP data, regional U.S. data suggest MRSA may account for greater than half of all *S. aureus* isolates [2, 4].

Hospital Length of Stay and Mortality

The primary outcome was 30-day mortality. Previous research has indicated that 30-day mortality is a more accurate measure of pneumonia-related mortality than 90-day mortality [16]. Admission and discharge dates were abstracted for each hospital stay and LOS was defined as the date of discharge minus the date of admission plus one day. Thirty-day and 90-day mortality were determined using date of death provided by the VHA status file. This method has a 98% exact agreement with the gold standard method (the National Death Index) to ascertain mortality [17].

Statistical Analysis

All statistical analyses were conducted using JMP 8.0® (SAS Corp., Cary, NC, USA) and Stata 10 (StataCorp, College Station, TX, USA). Due to the large sample size, we defined statistical significance as a two-tailed alpha ≤ 0.0001 for bivariate comparisons. In comparisons among the 3 treatment groups, GC-HCAP was used as the reference group and was compared to both the GC-CAP and non-GC groups. In multivariable logistic regression models, a two-tailed alpha ≤ 0.05 was used.

Patient demographics, baseline characteristics, comorbid conditions, bacterial pathogens, and mortality were compared between groups. Dichotomous variables were compared using chi-square tests or Fisher's exact tests. All continuous variables were tested for normality with the Shapiro-Wilk W test and were found to have non-normal distributions; therefore, comparisons

were performed with Wilcoxon rank sum tests. Chi-square and Kruskal-Wallis tests were used to compare differences in mortality and bacterial pathogens by the number of HCAP criteria per patient.

A generalized linear mixed-effect model with admitting hospital as a random effect was used to examine the association between the receipt of guideline-concordant antibiotics and 30-day mortality. To isolate the effects of guideline-concordant therapy (GC-HCAP *versus* GC-CAP), patients who received non-GC therapy were excluded from the model. The dependent variable was 30-day mortality and covariates included: patient sex, race, Hispanic ethnicity, individual HCAP risk factors, individual comorbid conditions, tobacco use, alcohol abuse or dependence, prescription for medications from selected medication classes in the previous 90 days, non-invasive mechanical ventilation, organ failure, and guideline-concordant antibiotic therapy. All covariates were considered to be clinically-relevant *a priori*. Because almost all patients with chronic kidney disease (CKD) as a comorbidity were on dialysis (98.5%), CKD was excluded from the model to avoid collinearity between variables.

To reduce potential bias in this non-randomized cohort, a propensity score for the receipt of GC-HCAP therapy *versus* GC-CAP therapy was calculated using a logistic regression model with guideline-concordant therapy as the dependent variable and all additional variables in the original model as covariates. Guideline-concordant antibiotic therapy and the propensity scores were included as covariates in a second multivariable logistic regression model with 30-day mortality as the dependent variable.

Results

Overall Population

Figure 1 provides a flow diagram with detailed information regarding exclusion criteria and the final cohort. Of the 62,682 patients with a principal *ICD-9-CM* discharge diagnosis code of pneumonia, a cohort of 15,071 met study inclusion criteria. Patients meeting inclusion criteria were then stratified by receipt of GC-HCAP (8.0%), GC-CAP (75.7%), or non-GC therapy (16.3%).

Patients were elderly (median age 76 years) and predominantly consisted of white males (82.1% white, 98.3% males), an innate characteristic of the majority of patients in the VHA [18, 19]. Nearly one-quarter of patients (23.1%) had more than one HCAP risk factor on admission. The most prevalent HCAP risk factor was hospitalization in the previous 90 days (66.3%). The median Charlson Index score was 3 (interquartile range [IQR], 2-5) and common comorbid conditions included chronic obstructive pulmonary disease (COPD) (56.6%), CKD (44.0%), diabetes (38.7%), heart failure (36.7%), and neoplastic disease (29.0%). Tobacco use was common (37.6%), and cardiovascular medications were the most prescribed medications in the 90 days prior to admission (76.1%). A small group of patients (1.2%) received non-invasive mechanical ventilation during admission. Table 2 lists additional baseline characteristics.

Baseline Characteristics, By Group

There were no significant differences between the GC-HCAP, GC-CAP, and non-GC groups in age, sex, or race. Charlson Index scores were similar between GC-HCAP and GC-CAP patients (median, IQR; 4, 2-6 *versus* 4, 2-5, $p<0.03$) and higher for GC-HCAP *versus* non-GC patients (median, IQR; 4, 2-*6 versus* 3, 2-5, $p<0.001$). At baseline, GC-CAP patients had a

higher prevalence of heart failure, COPD, tobacco use, and prescriptions for cardiovascular medications, inhaled corticosteroids, and pulmonary medications. GC-HCAP patients were more likely to have neoplastic disease. Organ failure did not differ significantly between GC-HCAP and GC-CAP patients.

HCAP Risk Factors

Overall, hospitalization in the previous 90 days was the most common HCAP risk factor (table 2). Compared to GC-CAP patients, GC-HCAP patients were more likely to have a recent hospitalization (77.7% *versus* 62.4%, $p<0.001$) and present with multiple HCAP risk factors (31.7% *versus* 21.5%, $p<0.001$). There were no differences between GC-HCAP and GC-CAP patients regarding nursing home residence in the previous 90 days, hemodialysis, or outpatient IV antibiotic therapy in the previous 90 days.

Guideline-Concordant Antibiotic Therapy

Most patients (83.7%) received antibiotic therapy concordant with either CAP or HCAP guidelines within 48 hours of hospital admission. The most common GC-HCAP antibiotic regimen included an antipseudomonal beta-lactam, an antipseudomonal fluoroquinolone, and either vancomycin or linezolid (82.1%). Most other GC-HCAP patients received a similar regimen including an antipseudomonal beta-lactam, an aminoglycoside, and an MRSA-active agent (21.7%). Patients receiving both an aminoglycoside and an antipseudomonal fluoroquinolone account for the overlap between the groups.

In GC-CAP patients, a respiratory fluoroquinolone was the most common regimen (67.1%), followed by beta-lactam plus macrolide (45.0%). A significant number of patients

prescribed GC-CAP antibiotics received both a respiratory fluoroquinolone and beta-lactam plus macrolide (15.5%). Nearly two-thirds (62.8%) of GC-CAP regimens included levofloxacin.

Non-GC patients received antibiotic regimens that did not meet minimum criteria for either CAP or HCAP guideline-concordance. Many of these patients received insufficient HCAP coverage, with single antipseudomonal coverage present in 47.8% and double antipseudomonal coverage present in 13.5%. One-third (30.9%) received either vancomycin or linezolid, and 25.2% received a combination of an MRSA-active agent and one antipseudomonal agent.

BACTERIAL PATHOGENS

Microorganisms were identified in 9.2% of patients (table 3). In patients with a positive culture, the most commonly isolated pathogens were *Streptococcus pneumoniae* (27.8%), *Staphylococcus aureus* (26.0%), *Pseudomonas aeruginosa* (14.4%), and *Haemophilus influenzae* (6.8%). Atypical organisms and anaerobes were rare (<3%).

Pseudomonas and *S. aureus* were identified more frequently in patients who received GC-HCAP *versus* GC-CAP therapy (24.4% *versus* 10.5%, $p<0.001$; and 38.7% *versus* 16.7%, $p<0.001$, respectively). Compared to GC-HCAP patients, GC-CAP patients were more likely to have a positive culture for *S. pneumoniae* (36.5% *versus* 14.2%, $p<0.001$) or *H. influenzae* (9.3% *versus* 0.9%, $p<0.001$). In non-GC patients, *S. aureus* and *Pseudomonas* were the most frequently isolated pathogens (40.8% and 17.4%, respectively). GC-HCAP and non-GC patients were similar without any statistically-significant differences in bacterial pathogens.

HEALTH OUTCOMES

Median hospital LOS was 5 days (IQR, 3-8 days) with 30-day and 90-day mortality rates of 12.6% and 23.3%, respectively (table 4). Compared to GC-CAP patients, GC-HCAP patients had a longer hospital LOS (median, IQR; 7, 4-13 *versus* 4, 3-7, $p<0.001$) and experienced higher rates of 30-day and 90-day mortality (22.8% *versus* 9.9%, $p<0.001$; 37.8% *versus* 19.8%, $p<0.001$, respectively). There were no significant differences in 30-day or 90-day mortality between GC-HCAP and non-GC patients; however, non-GC experienced shorter hospital LOS. Differences in mortality and hospital LOS remained the same when immunosuppressed patients (HIV/AIDS) were excluded from analyses.

Multilevel regression analysis of GC-HCAP and GC-CAP patients revealed several variables that were independently associated with 30-day mortality (table 5). The strongest independent predictors of 30-day mortality were hospital admission in the previous 90 days and GC-HCAP therapy (OR, 95% CI; 2.49, 2.12-2.94 and 2.18, 1.86-2.55, respectively). Other independent risk factors for 30-day mortality included cerebrovascular disease, neoplastic disease, non-invasive mechanical ventilation, neurological failure, renal failure, and hematologic failure. Tobacco use, recent prescription for cardiovascular medications, and recent prescription for inhaled corticosteroids were protective.

WHEN A PROPENSITY SCORE FOR RECEIPT OF GC-HCAP THERAPY WAS CALCULATED AND ENTERED INTO A SECOND MULTIVARIABLE LOGISTIC REGRESSION MODEL, GC-HCAP THERAPY CONTINUED TO BE AN INDEPENDENT RISK FACTOR FOR 30-DAY MORTALITY (OR 2.12, 95% CI 1.82-2.48).

KEY PATHOGENS AND HEALTH OUTCOMES, BY NUMBER OF HCAP RISK FACTORS

As the number of HCAP risk factors increased in an individual patient, changes were observed in pathogens and mortality (figures 2 and 3, respectively). Of particular interest, rates of pneumonia due to *S. aureus* and *Pseudomonas* increased as the number of HCAP risk factors increased from one to greater than two (*S. aureus*, 23.3% to 33.3%, $p<0.001$; *Pseudomonas*, 14.0% to 21.4%, $p=0.91$). Patient mortality followed a similar pattern. From one to greater than two risk factors, 30-day mortality increased from 11.6% to 17.2% ($p<0.001$), and 90-day mortality increased from 21.9% to 29.1% ($p<0.001$). Median hospital LOS was unchanged by the number of HCAP risk factors per patient.

Discussion

The present study compares the effect of GC-HCAP therapy and GC-CAP therapy on health outcomes of patients with HCAP. In this national cohort of non-critically-ill HCAP patients, GC-HCAP therapy did not result in decreased patient mortality or hospital LOS.

Multiple prior studies have characterized the HCAP population. HCAP patients are older, present with more severe disease, suffer worse health outcomes, and as suggested by limited U.S. data, may be more likely to present with MDR pathogens [2-6]. Table 6 summarizes the variation in selected HCAP pathogens among published data. Many similarities between HCAP patients in previous studies and HCAP patients in the present study were observed; however, mortality rates and hospital LOS were lower for HCAP patients in this study compared to previous research. This possibly reflects the exclusion of critically-ill patients, which may have resulted in less severe disease and improved outcomes compared to cohorts including critically-ill patients [9].

A limited number of HCAP studies have associated initial inappropriate antimicrobial therapy with increased mortality [4, 5, 20]. Two of these studies, one specific to only HCAP patients, determined that initial inappropriate therapy is an independent risk factor for in-hospital mortality [4, 20]. In contrast, Rello and colleagues recently evaluated HCAP and CAP patients with bacteremic pneumococcal pneumonia and demonstrated that despite low rates of inappropriate antibiotic therapy, mortality rates remained significantly higher in HCAP patients [21]. Higher mortality in an HCAP cohort with low rates of inappropriate therapy alludes to potential fundamental differences between patients with CAP and HCAP.

Current guidelines recommend that HCAP patients should be treated with antibiotics similar to those used in nosocomial pneumonia; however, there is currently no evidence to demonstrate that GC-HCAP antibiotics will improve the survival rates of HCAP patients. In 2009, El Solh and colleagues studied non-ICU pneumonia patients admitted to the hospital from nursing homes to compare differences in outcomes for those treated with GC-HCAP therapy and GC-CAP therapy [22]. No differences regarding in-hospital mortality or 30-day mortality were found between the GC-CAP and GC-HCAP groups, and GC-CAP patients actually had a decreased time to oral therapy and a decreased hospital LOS. Our analysis supports these notions regarding 30-day mortality and hospital LOS, and additionally, was not limited to only nursing home patients. In the present study, GC-HCAP therapy was not associated with improvements in patient LOS or mortality; in fact, GC-HCAP was associated with a longer LOS and increased mortality rates.

GC-HCAP and non-GC patients were mostly similar in baseline characteristics, pathogens, and mortality outcomes; however, non-GC patients experienced a two-day decrease in LOS. We attribute this to the fact that GC-HCAP regimens may be more complex to manage

and not as easily transferable to oral antibiotic therapy, similar to the GC-CAP population in the aforementioned El Solh study [22].

Despite great variation in HCAP pathogens throughout the published HCAP literature, HCAP patients consistently suffer at least double the mortality rate of CAP patients. Clinicians should be aware that these patients may be at an increased risk for poor outcomes; however, it is improper to mechanically prescribe broad-spectrum antibiotics to all patients with HCAP risk factors. Clinicians should be informed of their local epidemiology and use this information to afford a balance between appropriate empiric antibiotic therapy and overtreatment leading to resistance, increased adverse effects, and increased costs.

Even with guidelines and identified risk factors, the selection of patients that need coverage for MRSA and *Pseudomonas* still requires some subjectivity and sound clinical judgment. It is noteworthy that prescribers in our study were relatively successful, as demonstrated by initial antimicrobial therapy, at predicting bacterial pneumonia pathogens. Information from prior treatment (prior antibiotics or pathogens) may have played a role in decisions, but this information was not available. While it is reassuring to see the results, we are unable to elicit the reason for these prescriber tendencies.

We believe it is unlikely that GC-HCAP therapy itself was responsible for the detriment in LOS and mortality. Rather, we believe confounding factors not captured in our study, including severity of disease and functional status, likely influenced these differences. Prognostic scoring systems validated in CAP patients, such as the Pneumonia Severity Index and CURB-65, have demonstrated an increased mortality in patients with an increased severity of disease on admission [23, 24]. Use of these methods, along with the included Charlson Index scores, may have helped to explain mortality differences between treatment groups. Additionally, poor

functional status has proven to be a strong predictor of mortality and has been associated with an increased risk of resistant pathogens in pneumonia patients [25, 26]. A recent review of the concept of HCAP discusses the importance of functional status in pneumonia prognostication and suggests subgroups based on activities of daily living (ADL) scores may be useful in future classification systems [27].

It has also been proposed that physician- and/or patient-directed limitations on advanced care and aggressive intervention (e.g., ICU admission, invasive mechanical ventilation, and/or vasopressor therapy) may be partially responsible for increased mortality in some HCAP patients [21, 27]. By excluding patients with critical illness, we were able to potentially limit the amount it contributed to increased mortality; however, it is possible that physician decision and family wishes to limit aggressive intervention in terminally-ill patients could have affected mortality if these patients were not distributed equally between treatment groups.

Currently, two studies have evaluated the impact of individual HCAP risk factors on the risk of infection with a drug-resistant pathogen [7, 8]. Each group of investigators identified multiple individual risk factors that were independent predictors of pneumonia due to a resistant pathogen. Residence in a nursing home or long-term care facility was the only predictor common to both studies. Schreiber and colleagues also described an increased risk of resistant pathogens in patients with two or more HCAP risk factors compared to those with either one or zero risk factors [8]. Similarly, we described the impact of cumulative HCAP risk factors and found increased rates of *S. aureus* and *Pseudomonas* as patients possessed more HCAP criteria. Furthermore, we identified a positive correlation between the number of HCAP risk factors and patient mortality. Future research characterizing the negative effects of cumulative HCAP

criteria may help focus attention to the group of HCAP patients with the highest risk for poor outcomes.

While the current study provides valuable information among a national patient cohort, there are limitations. First, it was a retrospective cohort study in a predominantly elderly male population and is subject to the inherent limitations of all retrospective research. Multilevel regression techniques and propensity scores were used in attempt to account for confounders and limit any potential biases; however, these methods were unable to fully account for all confounders and are not equivalent to the strengths of a prospective, randomized study.

Second, the use of *ICD-9-CM* codes to identify pneumonia patients, pathogens, and baseline characteristics can be potentially problematic. This approach is common in large database studies and often necessary to enable efficient data collection. Many current HCAP studies are limited by single-center or regional study sites and relatively small sample sizes. The use of *ICD-9-CM* codes enabled us to obtain significant amounts of information from a large national cohort of patients in a closed health system, a major strength of this study. The process of medical coding introduces several opportunities for human error and potential bias; however, data analyzing *ICD-9-CM* codes for inpatient pneumonia patients have favorable positive and negative predictive values (85.5% and 97.2%, respectively), indicating a relatively low likelihood of misclassification [28].

Third, the culture-positive rate in our study is relatively low. Culture-positive rates vary widely between pneumonia studies, and our data probably reflects a reliance on sputum cultures in our population of non-critically-ill patients. Previous research demonstrates the difficulty of procuring good quality sputum samples with definitive results, as well as the lower culture-positive rate seen among non-critically-ill patients [9, 29].

Fourth, we were unable to compare differences in functional status between treatment groups. While functional status is not often measured in pneumonia studies, there is evidence that poor functional status can result in poor outcomes [25]. When possible, future HCAP studies should include functional status to further quantify the effects it may have on bacterial pathogens and outcomes.

Lastly, it would be useful to have more detailed data on antibiotic timing and bacterial susceptibility. Part of the inclusion criteria for our study was receipt of initial antibiotic therapy within 48 hours; however, we have no further data on antibiotic timing within that window. Additionally, no data were provided on bacterial susceptibility or rates of methicillin-resistance in patients with positive cultures for *S. aureus*. MRSA is a pathogen of interest in HCAP cohorts, but *ICD-9-CM* codes from 2002-2007 did not differentiate between methicillin-sensitive and methicillin-resistant *S. aureus*. Consequently, without bacterial susceptibilities, we were unable to identify and compare patients who were escalated to appropriate antibiotic therapy after receiving initial inappropriate therapy.

In conclusion, guideline-concordant HCAP antibiotic therapy was not associated with improved 30-day mortality in this U.S. cohort of non-critically-ill VHA HCAP patients. Additional research is needed to fully understand reasons for mortality in HCAP patients and to determine interventions that improve survival.

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Table 1: Definitions of CAP and HCAP Guideline-Concordant Therapy (Non-ICU Patients)

Guideline-Concordant CAP Therapy	Guideline-Concordant HCAP Therapy
Beta-lactam[1] *plus* macrolide[2*]	Antipseudomonal beta-lactam[4†] *plus* antipseudomonal fluoroquinolone[5] *plus* vancomycin *or* linezolid
Respiratory fluoroquinolone[3]	Antipseudomonal beta-lactam[4†] *plus* aminoglycoside[6] *plus* vancomycin *or* linezolid

CAP: community-acquired pneumonia; HCAP: healthcare-associated pneumonia; ICU: intensive care unit; [*]: Doxycycline may be substituted for macrolide; [†]: Aztreonam may be substituted for antipseudomonal beta-lactam in penicillin-allergic patients; [1]: Beta-lactam includes cefotaxime, ceftriaxone, ampicillin, or ertapenem; [2]: Macrolide includes azithromycin, clarithromycin, or erythromycin; [3]: Respiratory fluoroquinolone includes moxifloxacin, levofloxacin, or gatifloxacin; [4]: Antipseudomonal beta-lactam includes cefepime, ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanate; [5]: Antipseudomonal fluoroquinolone includes ciprofloxacin or levofloxacin; [6]: Aminoglycoside includes gentamicin, tobramycin, or amikacin.

TABLE 2: BASELINE CHARACTERISTICS

Patient Characteristics	**Overall (n=15,071)**	**GC-HCAP (n=1,211)**	**GC-CAP (n=11,408)**	**Non-GC (n=2,452)**	**GC-HCAP *versus* GC-CAP (p-value)**	**GC-HCAP *versus* Non-GC (p-value)**
Age in years; median, IQR	76, 70–80	76, 70–80	76, 70–80	76, 70–81	0.74	0.45
Male, %	98.3	98.2	98.4	98.2	0.61	0.89
Race, %					0.02	0.04
White	82.1	79.4	82.5	81.3		
Black	13.4	15.5	13.3	12.6		
Other	4.5	5.1	4.2	6.0		
Hispanic ethnicity, %	7.2	13.1	5.8	10.6	**<0.001**	0.02
HCAP Risk Factors, %						
Recent hospitalization, 90d	66.3	77.7	62.4	78.9	**<0.001**	0.42
Nursing home resident, 90d	2.9	3.0	2.8	3.5	0.71	0.36
Hemodialysis	43.4	42.4	45.5	33.9	0.04	**<0.001**

Outpatient IV antibiotic therapy, 90d	12.1	12.6	11.9	12.4	0.53	0.89
≥2 HCAP Risk Factors, %	22.6	31.1	21.0	25.7	**<0.001**	0.001
Charlson Index score; median, IQR	3, 2–5	4, 2–6	4, 2–5	3, 2–5	0.03	**<0.001**
Comorbid conditions, %						
Myocardial infarction	10.3	10.0	10.2	11.3	0.83	0.25
Heart failure	36.7	31.5	37.8	34.3	**<0.001**	0.09
Cerebrovascular disease	23.0	24.9	22.4	24.6	0.05	0.84
COPD	56.6	50.7	58.0	52.6	**<0.001**	0.28
Liver disease	1.4	1.3	1.3	1.5	0.95	0.72
CKD	44.0	43.2	46.1	34.8	0.05	**<0.001**
Diabetes	38.7	41.6	38.7	37.4	0.05	0.01
Neoplastic disease	29.0	35.8	28.0	30.4	**<0.001**	0.001
HIV/AIDS	0.3	0.3	0.3	0.4	0.56	0.86
Substance abuse or dependence						
Tobacco use	37.6	33.1	38.9	33.9	**<0.001**	0.62
Alcohol abuse or dependence	4.9	4.0	4.8	5.8	0.26	0.03

Medication use, 90d, %						
Cardiovascular medications	76.1	65.7	78.9	68.3	**<0.001**	0.12
Antidiabetic medications	26.8	25.5	27.5	24.3	0.14	0.41
Inhaled corticosteroids	25.0	19.5	26.4	20.9	**<0.001**	0.31
Systemic corticosteroids	29.6	26.5	30.5	26.5	0.003	0.98
Pulmonary medications	41.9	35.6	43.6	37.1	**<0.001**	0.38
Non-invasive mechanical ventilation, %	1.2	2.0	1.1	1.0	0.01	0.01
Organ failure, %						
Any organ failure	18.0	22.0	17.9	16.4	0.001	**<0.001**
Neurological	1.6	1.7	1.5	2.0	0.77	0.52
Renal	17.6	21.9	17.6	15.7	0.0002	**<0.001**
Hematologic	2.3	2.6	2.2	2.7	0.29	0.99
Hepatic	0.2	0.2	0.2	0.2	0.74	0.72

GC-HCAP: guideline-concordant healthcare-associated pneumonia; GC-CAP: guideline-concordant community-acquired pneumonia; GC: guideline-concordant; IQR: interquartile range; HCAP: healthcare-associated pneumonia; IV: intravenous; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome

TABLE 3: BACTERIAL PATHOGEN DISTRIBUTION FOR GC-HCAP, GC-CAP, AND NON-GC PATIENTS

Patient Characteristics	**Overall**	**GC-HCAP**	**GC-CAP**	**Non-GC**	**GC-HCAP *versus* GC-CAP (p-value)**	**GC-HCAP *versus* Non-GC (p-value)**
All patients, n	15,071	1,211	11,408	2,452		
Organism identified	9.2	18.6	7.3	13.6	**<0.001**	**<0.001**
Single organism identified	8.0	15.9	6.6	10.7	**<0.001**	**<0.001**
Multiple organisms identified	1.2	2.7	0.7	2.9	**<0.001**	0.77
Culture-positive patients, n	1390	225	832	333		
Gram-positive pathogens						
S. pneumoniae	27.8	14.2	36.5	15.0	**<0.001**	0.80
Streptococcus, other	4.6	3.1	5.6	3.0	0.13	0.94
Staphylococcus aureus	26.0	38.7	16.7	40.8	**<0.001**	0.61
Gram-negative pathogens						
K. pneumoniae	5.4	7.1	4.7	6.0	0.15	0.60
Pseudomonas	14.4	24.4	10.5	17.4	**<0.001**	0.04

H. influenzae	6.8	0.9	9.3	4.5	**<0.001**	0.01
E. coli	1.6	1.8	1.3	2.1	0.54	0.54
Other gram-negatives	5.5	5.3	5.0	6.6	0.86	0.79
Atypical pathogens						
Legionella	1.2	0	1.6	0.9	0.08	0.28
Mycoplasma	0.6	0.4	0.6	0.6	1.00	1.00
Chlamydia	0.1	0	0.1	0	1.00	--
Anaerobes	0.8	0.4	1.0	0.6	0.69	1.0000

GC-HCAP: guideline-concordant healthcare-associated pneumonia; GC-CAP: guideline-concordant community-acquired pneumonia; GC: guideline-concordant.

TABLE 4: HEALTH OUTCOMES FOR GC-HCAP, GC-CAP, AND NON-GC PATIENTS

Health Outcomes	**Overall (n=15,071)**	**GC-HCAP (n=1,211)**	**GC-CAP (n=11,408)**	**Non-GC (n=2,452)**	**GC-HCAP *versus* GC-CAP (p-value)**	**GC-HCAP *versus* Non-GC (p-value)**
Length of stay in days; median, IQR	5, 3 – 8	7, 4 – 13	4, 3 – 7	5, 3 – 9	**<0.001**	**<0.001**
30-day mortality, %	12.6	22.8	9.9	20.1	**<0.001**	0.06
90-day mortality, %	23.3	37.8	19.8	32.7	**<0.001**	0.002

GC-HCAP: guideline-concordant healthcare-associated pneumonia; GC-CAP: guideline-concordant community-acquired pneumonia; GC: guideline-concordant; IQR: interquartile range.

TABLE 5: RISK FACTORS FOR 30-DAY MORTALITY IN GC-HCAP AND GC-CAP PATIENTS

Risk Factors*	**Odds Ratio**	**95% Confidence Interval**	**p-value**
Sex	0.96	0.62 - 1.48	0.84
Race	1.11	0.99 - 1.24	0.08
Hispanic ethnicity	0.84	0.62 - 1.14	0.26
HCAP risk factors			
Recent hospital admission, 90d	**2.49**	**2.12 - 2.94**	**<0.001**
Nursing home admission, 90d	0.84	0.56 - 1.26	0.40
Hemodialysis	1.13	0.98 - 1.31	0.10
Outpatient IV antibiotics, 90d	1.05	0.87 - 1.27	0.63
Comorbid conditions			
Myocardial infarction	0.94	0.77 - 1.15	0.57
Heart failure	1.03	0.90 - 1.17	0.69
Cerebrovascular disease	**1.20**	**1.05 - 1.37**	**0.01**
COPD	0.92	0.80 - 1.06	0.28
Liver disease	1.02	0.62 - 1.68	0.94
Diabetes	0.85	0.72 - 1.01	0.07
Neoplastic disease	**1.67**	**1.48 - 1.89**	**<0.001**
HIV/AIDS	1.12	0.39 - 3.28	0.83
Substance abuse or dependence			
Tobacco use	**0.73**	**0.64 - 0.83**	**<0.001**
Alcohol abuse	1.11	0.85 - 1.44	0.46

Medication use, by class			
Cardiovascular medications	**0.67**	**0.58 - 0.76**	**<0.001**
Antidiabetic medications	0.89	0.73 - 1.08	0.23
Inhaled corticosteroids	**0.70**	**0.59 - 0.82**	**<0.001**
Systemic corticosteroids	1.02	0.88 - 1.17	0.83
Pulmonary medications	1.04	0.89 - 1.20	0.65
Non-invasive mechanical ventilation	**1.75**	**1.12 - 2.74**	**0.01**
Organ failure			
Neurological	**1.52**	**1.03 - 2.26**	**0.04**
Renal	**1.36**	**1.16 - 1.59**	**<0.001**
Hematologic	**1.80**	**1.31 - 2.48**	**<0.001**
Hepatic	2.21	0.83 - 5.87	0.11
GC-HCAP *versus* GC-CAP	**2.18**	**1.86 - 2.55**	**<0.001**

GC-HCAP: guideline-concordant healthcare-associated pneumonia; GC-CAP: guideline-concordant community-acquired pneumonia; HCAP: healthcare-associated pneumonia; IV: intravenous; COPD: chronic obstructive pulmonary disease; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome; [*]: variables were ordered to compare presence *versus* absence of characteristic when possible; patient sex and race were ordered as male *versus* female and black *versus* non-black, respectively.

Table 6: Variation in Selected HCAP Pathogens, By Publication

Pathogen (%, culture-positive)	**Kollef 2005 (n=988)**	**Carratalà 2007 (n=126)**	**Micek 2007 (n=431)**	**Shindo 2009 (n=141)**	**Attridge 2011 (n=1,211)**
S. pneumoniae	5.5	27.8	10.4	13.5	14.2
S. aureus	46.7	2.4	44.5	9.9	26.0
MRSA (% of total *S. aureus*)	56.8	0	68.8	35.7	--
P. aeruginosa	25.3	1.6	25.5	5.7	24.4

MRSA = methicillin-resistant *Staphylococcus aureus*

FIGURE 1: PATIENT INCLUSION AND EXCLUSION FLOW DIAGRAM

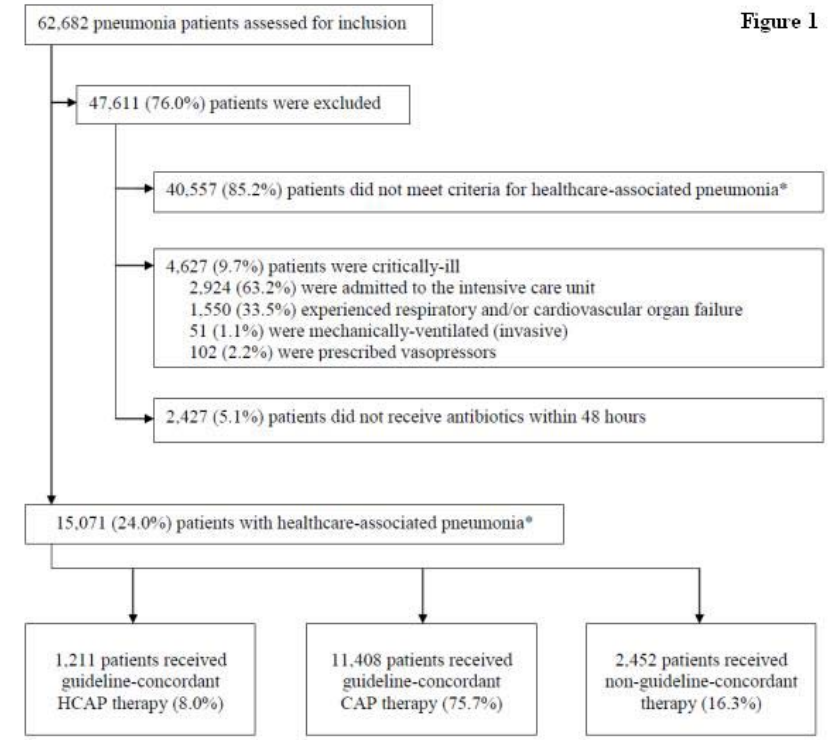

FIGURE 2: BACTERIAL PATHOGENS IN CULTURE-POSITIVE HCAP PATIENTS, BY NUMBER OF HCAP RISK FACTORS (N=1,390)

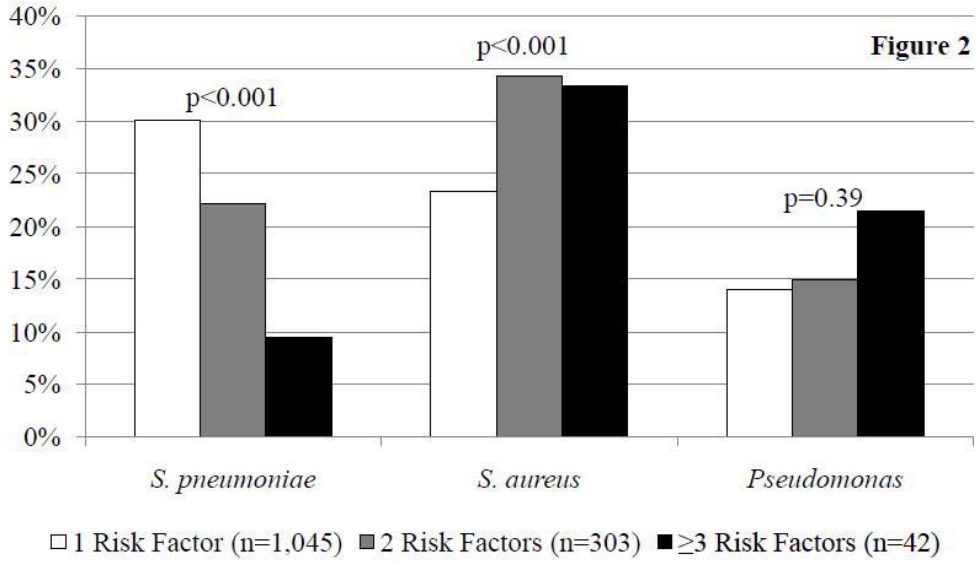

FIGURE 3: 30-DAY AND 90-DAY MORTALITY IN HCAP PATIENTS, BY NUMBER OF HCAP RISK FACTORS (N=15,071)