Treatment Trends and Outcomes in Healthcare-Associated Pneumonia

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BACKGROUND: The American Thoracic Society and Infectious Diseases Society of America guidelines for management of healthcare-associated pneumonia (HCAP), first published in 2005, have been controversial regarding the selection of empiric broad-spectrum antibiotics, whether the criteria for HCAP predicts the likelihood of infection with multidrug resistant organisms, and whether HCAP patients have improved outcomes when treated with empiric broad-spectrum antibiotics.

METHODS: A retrospective cohort study at 488 US hospitals from July 2007 to November 2011. Patients who met criteria for HCAP were included. Guideline-concordant antibiotics were assessed based on guideline recommendations. We assessed changes in hospital rates of concordant antibiotic use over time and their correlation with outcomes.

RESULTS: Among 149,963 patients with HCAP, 19.6% received fully guideline-concordant antibiotics, 21.7% received partially concordant antibiotics, and 58.9% received discordant antibiotics. Guideline concordance increased over time. Rates of fully or partially concordant antibiotics varied across hospitals (median 36.4%; interquartile range 25.8%-49.1%). Among patients who received discordant antibiotics, 81.5% were treated according to community-acquired pneumonia (CAP) guidelines. On average, the rate of guideline concordance increased by 2.2% per 6-month interval, while hospital level rates of mortality, excess length of stay, and progression to respiratory failure did not change.

CONCLUSIONS: In this large, nationally representative cohort, only 1 in 5 patients with risk factors for HCAP received treatment that was fully in accordance with guidelines, and many received CAP therapy instead. At the hospital level, increases in the use of concordant antibiotics were not associated with declines in mortality, excess length of stay, or progression to respiratory failure. *Journal of Hospital Medicine* 2017;12: 886-891. © 2017 Society of Hospital Medicine

Bacterial pneumonia remains an important cause of morbidity and mortality in the United States, and is the 8th leading cause of death with 55,227 deaths among adults annually.[1] In 2005, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) collaborated to update guidelines for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia, and healthcare-associated pneumonia (HCAP).[2] This broad document outlines an evidence-based approach to diagnostic testing and antibiotic management based on the epidemiology and risk factors for these conditions. The guideline specifies the following criteria for HCAP: hospitalization in the past 90 days, residence in a skilled nursing facility (SNF), home infusion therapy, hemodialysis, home wound care, family members with multidrug resistant organisms (MDRO), and immunosuppressive diseases or medications, with the presumption that these patients are more likely to be harboring MDRO and should thus be treated empirically with broad-spectrum antibiotic therapy. Prior studies have shown that patients with HCAP have a more severe illness, are more likely to have MDRO, are more likely to be inadequately treated, and are at a higher risk for mortality than patients with community-acquired pneumonia (CAP).[3,4]

These guidelines are controversial, especially in regard to the recommendations to empirically treat broadly with 2 antibiotics targeting *Pseudomonas* species, whether patients with HCAP merit broader spectrum coverage than patients with CAP, and whether the criteria for defining HCAP are adequate to predict which patients are harboring MDRO. It has subsequently been proposed that HCAP is more related to CAP than to HAP, and a recent update to the guideline removed recommendations for treatment of HCAP and will be placing HCAP into the guidelines for CAP instead.[5] We sought to investigate the degree of uptake of the ATS and IDSA guideline recommendations by physicians over time, and whether this led to a change in outcomes among patients who met the criteria for HCAP.

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METHODS

Setting and Patients

We identified patients discharged between July 1, 2007, and November 30, 2011, from 488 US hospitals that participated in the Premier database (Premier Inc., Charlotte, North Carolina), an inpatient database developed for measuring quality and healthcare utilization. The database is frequently used for healthcare research and has been described previously.[6] Member hospitals are in all regions of the US and are generally reflective of US hospitals. This database contains multiple data elements, including sociodemographic information, *International Classification of Diseases, 9th Revision-Clinical Modification* (ICD-9-CM) diagnosis and procedure codes, hospital and physician information, source of admission, and discharge status. It also includes a date-stamped log of all billed items and services, including diagnostic tests, medications, and other treatments. Because the data do not contain identifiable information, the institutional review board at our medical center determined that this study did not constitute human subjects research.

We included all patients aged ≥18 years with a principal diagnosis of pneumonia or with a secondary diagnosis of pneumonia paired with a principal diagnosis of respiratory failure, acute respiratory distress syndrome, respiratory arrest, sepsis, or influenza. Patients were excluded if they were transferred to or from another acute care institution, had a length of stay of 1 day or less, had cystic fibrosis, did not have a chest radiograph, or did not receive antibiotics within 48 hours of admission.

For each patient, we extracted age, gender, principal diagnosis, comorbidities, and the specialty of the attending physician. Comorbidities were identified from ICD-9-CM secondary diagnosis codes and Diagnosis Related Groups by using Healthcare Cost and Utilization Project Comorbidity Software, version 3.1, based on the work of Elixhauser (Agency for Healthcare Research and Quality, Rockville, Maryland).[7] In order to ensure that patients had HCAP, we required the presence of ≥1 HCAP criteria, including hospitalization in the past 90 days, hemodialysis, admission from an SNF, or immune suppression (which was derived from either a secondary diagnosis for neutropenia, hematological malignancy, organ transplant, acquired immunodeficiency virus, or receiving immunosuppressant drugs or corticosteroids [equivalent to ≥20 mg/day of prednisone]).

Definitions of Guideline-Concordant and Discordant Antibiotic Therapy

The ATS and IDSA guidelines recommended the following antibiotic combinations for HCAP: an antipseudomonal cephalosporin or carbapenem or a beta-lactam/lactamase inhibitor, plus an antipseudomonal quinolone or aminoglycoside, plus an antibiotic with activity versus methicillin resistant *Staphylococcus aureus* (MRSA), such as vancomycin or linezolid. Based on these guidelines, we defined the receipt of fully guideline-concordant antibiotics as 2 recommended antibiotics for *Pseudomonas* species plus 1 for MRSA administered by the second day of admission. Partially guideline-concordant antibiotics were defined as 1 recommended antibiotic for *Pseudomonas* species plus 1 for MRSA by the second day of hospitalization. Guideline-discordant antibiotics were defined as all other combinations.

Statistical Analysis

Descriptive statistics on patient characteristics are presented as frequency, proportions for categorical factors, and median with interquartile range (IQR) for continuous variables for the full cohort and by treatment group, defined as fully or partially guideline-concordant antibiotic therapy or discordant therapy. Hospital rates of fully guideline-concordant treatment are presented overall and by hospital characteristics. The association of hospital characteristics with rates of fully guideline-concordant therapy were assessed by using 1-way analysis of variance tests.

To assess trends across hospitals for the association between the use of guideline-concordant therapy and mortality, progression to respiratory failure as measured by the late initiation of invasive mechanical ventilation (day 3 or later), and the length of stay among survivors, we divided the 4.5-year study period into 9 intervals of 6 months each; 292 hospitals that submitted data for all 9 time points were examined in this analysis. Based on the distribution of length of stay in the first time period, we created an indicator variable for extended length of stay with length of stay at or above the 75th percentile, defined as extended. For each hospital at each 6-month interval, we then computed risk-standardized guideline-concordant treatment (RS-treatment) rates and risk-standardized in-hospital outcome rates similar to methods used by the Centers for Medicare and Medicaid Services for public reporting.[8] For each hospital at each time interval, we estimated a predicted rate of guideline-concordant treatment as the sum of predicted probabilities of guideline-concordant treatment from patient factors and the random intercept for the hospital in which they were admitted. We then calculated the expected rate of guideline-concordant treatment as the sum of expected probabilities of treatment received from patient factors only. RS-treatment was then calculated as the ratio of predicted to expected rates multiplied by the overall unadjusted mean treatment rate from all patients.[9] We repeated the same modeling strategy to calculate risk-standardized outcome (RS-outcome) rates for each hospital across all time points. All models were adjusted for patient demographics and comorbidities. Similar models using administrative data have moderate discrimination for mortality.[10]

We then fit mixed-effects linear models with random hospital intercept and slope across time for the RS-treatment and outcome rates, respectively. From these models, we estimated the mean slope for RS-treatment and for RS-outcome over time. In addition, we estimated a slope or trend over time for each hospital for treatment and for outcome and evaluated the correlation between the treatment and outcome trends.

TABLE. Antibiotics Received Among Patients Given Fully Guideline-Concordant, Partially Guideline-Concordant, or Guideline-Discordant Antibiotics for HCAP

Early Antibiotics (Days 0/1/2)	Overall	HCAP Fully Guideline-Concordant	HCAP Partially Guideline-Concordant	HCAP Guideline-Discordant	*P* Valuea
	n (%)	n (%)	n (%)	n (%)	
	149,963 (100)	29,359 (19.6)	32,604 (21.7)	88,000 (58.9)	
Vancomycin	63,480 (42.3)	27,466 (93.6)	30,484 (93.5)	5530 (6.3)	<.0001
Linezolid	6429 (4.3)	2877 (9.8)	3090 (9.5)	462 (0.5)	<.0001
Antipseudomonal carbapenem	11,344 (7.6)	4505 (15.3)	3802 (11.7)	3037 (3.5)	<.0001
Nonpseudomonal carbapenem	1328 (0.9)	173 (0.6)	807 (2.5)	807 (0.9)	<.0001
Third generation cephalosporin (without activity vs Pseudomonas sp.)	56,079 (37.4)	4704 (16.0)	8153 (25.0)	43,222 (49.1)	<.0001
Antipseudomonal cephalosporin	20,615 (13.8)	7274 (24.8)	6319 (19.4)	7022 (8.0)	<.0001
Antipseudomonal beta-lactam/lactamase inhibitor	53,284 (35.5)	18,507 (63.0)	16,474 (50.5)	18,303 (20.8)	<.0001
Aztreonam	5546 (3.7)	2609 (8.9)	1435 (4.4)	1502 (1.7)	<.0001
Nonpseudomonal beta-lactam/lactamase inhibitor	1501 (1.0)	173 (0.6)	311 (1.0)	1017 (1.2)	<.0001
Beta-lactam	315 (0.2)	59 (0.2)	96 (0.3)	160 (0.2)	.001
Respiratory quinolone	76,262 (50.9)	19,743 (67.2)	10,232 (31.4)	46,287 (52.6)	<.0001
Antipseudomonal quinolone	69,668 (46.5)	25,952 (88.4)	6748 (20.7)	36,968 (42.0)	<.0001
Macrolide	49,846 (33.2)	4390 (15.0)	8236 (25.3)	37,220 (42.3)	<.0001
Doxycycline	2805 (1.9)	375 (1.3)	528 (1.6)	1902 (2.2)	<.0001
Aminoglycoside	8076 (5.4)	4887 (16.6)	1065 (3.3)	2124 (2.4)	<.0001

[a]*P*-value from Chi-square test

NOTE: Abbreviation: HCAP, heathcare-associated pneumonia.

All analyses were performed using the Statistical Analysis System version 9.4 (SAS Institute Inc., Cary, NC) and STATA release 13 (StataCorp, LLC, College Station, Texas).

RESULTS

Of 1,601,064 patients with a diagnosis of pneumonia in our dataset, 436,483 patients met our inclusion criteria, and of those, 149,963 (34.4%) met at least 1 HCAP criterion and were included as our study cohort (supplementary Figure). Among the study cohort, the median age was 73 years (IQR, 61-83), 51.4% of patients were female, 69.6% of patients were white, and a majority of patients (76.2 %) were covered by Medicare. HCAP categories included hospitalization in the past 90 days (63.1%), hemodialysis (12.8%), admission from a SNF (23.6%), and immunosuppression (28.9%). One-quarter of the patients were treated in the intensive care unit (ICU) by day 2 of their hospitalization. The most common comorbidities were hypertension (65.1%), chronic obstructive pulmonary disease (47.3%), anemia (40.9%), diabetes (36.6%), and congestive heart failure (35.7%). Pneumonia was the principal diagnosis in 61.9% of patients, and sepsis was the principal diagnosis in 29.3% of patients. The unadjusted median length of stay was 6 days, the median cost was $10,049, and the in-hospital mortality was 11.1%. Patients who received fully or partially guideline-concordant antibiotics were younger on average and had a higher combined comorbidity score, and they were more likely to have been admitted to the ICU and to have received vasopressor medications and mechanical ventilation. They also had higher unadjusted mortality, longer lengths of stay, and higher costs (see supplemental Table 1 for more details).

The Table shows the antibiotics received by patients. Overall, 19.6% of patients received fully guideline-concordant treatment, 21.7% received partially guideline-concordant treatment, and the remaining 58.9% received guideline-discordant antibiotics. Among the guideline-discordant patients, 81.5% were treated according to CAP guidelines instead. Next, we examined the degree to which guide-

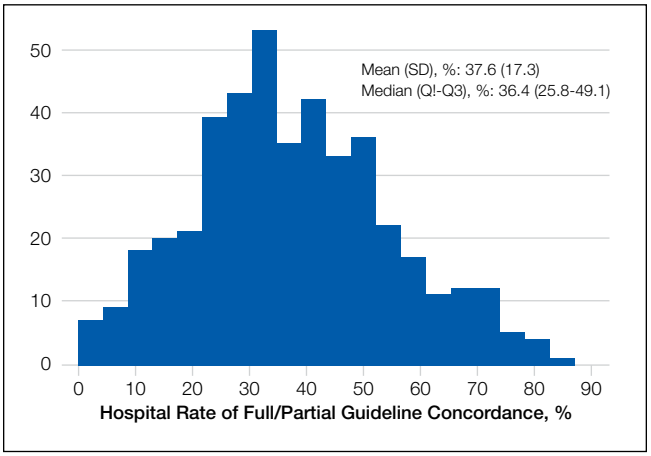

FIG 1. Distribution of rates of compliance with administering guideline-concordant antibiotics among hospitals. The X axis shows the rate that hospitals are compliant with prescribing at least partially guideline concordant antibiotics (ie, the percent of HCAP patients at a hospital who receive at least partially concordant antibiotics), and the Y axis shows the number of hospitals with each rate of compliance.

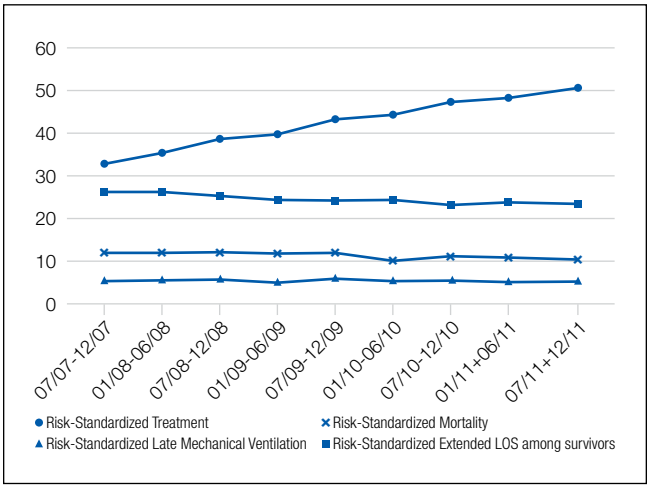

FIG 2. Trends in Risk-Standardized Guideline-concordant treatment and Risk-Standardized outcomes.

line-concordant antibiotics were prescribed at the hospital level. Figure 1 shows the distribution of hospital rates of administering at least partially guideline-concordant therapy. Rates range from 0% to 87.1%, with a median of 36.4%. Hospital-level characteristics associated with administering higher rates of at least partially guideline-concordant antibiotics included larger size, urban location, and being a teaching institution (supplementary Table 2). Overall, physician adherence to guideline-recommended empiric antibiotic therapy slowly increased over the 4-year study period with no indication of a plateau (Figure 2, top line).

Next, we examined the outcomes associated with the administration of guideline-concordant antibiotics at the hospital level. Among the 488 hospitals, there were 292 hospitals for which we had data over the entire study period, which included 121,600 patients. Among these patients, 49,445 (40.7%) received guideline-concordant antibiotics and 72,155 (59.3%) received guideline-discordant antibiotics. On average, the rate of guideline concordance increased by 2.2% per 6-month interval, while mortality fell by 0.24% per interval. After adjustment for patient demographics and comorbidities at the hospital level, there was no significant correlation between increases in concordant antibiotic prescribing rates and hospital mortality (Pearson correlation = −0.064; $P = 0.28$), progression to respiratory failure (ie, late initiation of intermittent mandatory ventilation; Pearson correlation = 0.084; $P = 0.15$), or extended length of stay among survivors (Pearson correlation = 0.10; $P = 0.08$; Figure 2).

DISCUSSION

In this large, retrospective cohort study, we found that there was a substantial gap between the empiric antibiotics recommended by the ATS and IDSA guidelines and the empiric antibiotics that patients actually received. Over the study period, we saw an increased adherence to guidelines, in spite of growing evidence that HCAP risk factors do not adequately predict which patients are at risk for infection with an MDRO.[11] We used this change in antibiotic prescribing behavior over time to determine if there was a clinical impact on patient outcomes and found that at the hospital level, there were no improvements in mortality, excess length of stay, or progression to respiratory failure despite a doubling in guideline-concordant antibiotic use.

At least 2 other large studies have assessed the association between guideline-concordant therapy and outcomes in HCAP.[12,13] Both found that guideline-concordant therapy was associated with increased mortality, despite propensity matching. Both were conducted at the individual patient level by using administrative data, and results were likely affected by unmeasured clinical confounders, with sicker patients being more likely to receive guideline-concordant therapy. Our focus on the outcomes at the hospital level avoids this selection bias because the overall severity of illness of patients at any given hospital would not be expected to change over the study period, while physician uptake of antibiotic prescribing guidelines would be expected to increase over time. Determining the correlation between increases in guideline adherence and changes in patient outcome may offer a better assessment of the impact of guideline adherence. In this regard, our results are similar to those achieved by 1 quality improvement collaborative that was aimed at increasing guideline concordant therapy in ICUs. Despite an increase in guideline concordance from 33% to 47% of patients, they found no change in overall mortality.[14]

There were several limitations to our study. We did not have access to microbiologic data, so we were unable to determine which patients had MDRO infection or determine antibiotic-pathogen matching. However, the treating physicians in our study population presumably did not have access to this data at the time of treatment either because the time period we examined was within the first 48 hours of hospi-

talization, the interval during which cultures are incubating and the patients are being treated empirically. In addition, there may have been HCAP patients that we failed to identify, such as patients who were admitted in the past 90 days to a hospital that does not submit data to Premier. However, it is unlikely that prescribing for such patients should differ systematically from what we observed. While the database draws from 488 hospitals nationwide, it is possible that practices may be different at facilities that are not contained within the Premier database, such as Veterans Administration Hospitals. Similarly, we did not have readings for chest x-rays; hence, there could be some patients in the dataset who did not have pneumonia. However, we tried to overcome this by including only those patients with a principal diagnosis of pneumonia or sepsis with a secondary pneumonia diagnosis, a chest x-ray, and antibiotics administered within the first 48 hours of admission.

There are likely several reasons why so few HCAP patients in our study received guideline-concordant antibiotics. A lack of knowledge about the ATS and IDSA guidelines may have impacted the physicians in our study population. El-Solh et al.[15] surveyed physicians about the ATS-IDSA guidelines 4 years after publication and found that only 45% were familiar with the document. We found that the rate of prescribing at least partially guideline-concordant antibiotics rose steadily over time, supporting the idea that the newness of the guidelines was 1 barrier. Additionally, prior studies have shown that many physicians may not agree with or choose to follow guidelines, with only 20% of physicians indicating that guidelines have a major impact on their clinical decision making,[16] and the majority do not choose HCAP guideline-concordant antibiotics when tested.[17] Alternatively, clinicians may not follow the guidelines because of a belief that the HCAP criteria do not adequately indicate patients who are at risk for MDRO. Previous studies have demonstrated the relative inability of HCAP risk factors to predict patients who harbor MDRO[18] and suggest that better tools such as clinical scoring systems, which include not only the traditional HCAP risk factors but also prior exposure to antibiotics, prior culture data, and a cumulative assessment of both intrinsic and extrinsic factors, could more accurately predict MDRO and lead to a more judicious use of broad-spectrum antimicrobial agents.[19-25] Indeed, these collective findings have led the authors of the recently updated guidelines to remove HCAP as a clinical entity from the hospital-acquired or ventilator-associated pneumonia guidelines and place them instead in the upcoming updated guidelines on the management of CAP.[5] Of these 3 explanations, the lack of familiarity fits best with our observation that guideline-concordant therapy increased steadily over time with no evidence of reaching a plateau. Ironically, as consensus was building that HCAP is a poor marker for MDROs, routine empiric treatment with vancomycin and piperacillin-tazobactam ("vanco and zosyn") have become routine in many hospitals. Additional studies are needed to know if this trend has stabilized or reversed.

CONCLUSIONS

In conclusion, clinicians in our large, nationally representative sample treated the majority of HCAP patients as though they had CAP. Although there was an increase in the administration of guideline-concordant therapy over time, this increase was not associated with improved outcomes. This study supports the growing consensus that HCAP criteria do not accurately predict which patients benefit from broad-spectrum antibiotics for pneumonia, and most patients fare well with antibiotics targeting common community-acquired organisms.

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