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MAJOR ARTICLE

Antibiotic Prescribing for Adults Hospitalized in the Etiology of Pneumonia in the Community Study

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Background. Community-acquired pneumonia (CAP) 2007 guidelines from the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) recommend a respiratory fluoroquinolone or beta-lactam plus macrolide as first-line antibiotics for adults hospitalized with CAP. Few studies have assessed guideline-concordant antibiotic use for patients hospitalized with CAP after the 2007 IDSA/ATS guidelines. We examine antibiotics prescribed and associated factors in adults hospitalized with CAP.

Methods. From January 2010 to June 2012, adults hospitalized with clinical and radiographic CAP were enrolled in a prospective Etiology of Pneumonia in the Community study across 5 US hospitals. Patients were interviewed using a standardized questionnaire, and medical charts were reviewed. Antibiotics prescribed were classified according to defined nonrecommended CAP antibiotics. We assessed factors associated with nonrecommended CAP antibiotics using logistic regression.

Results. Among enrollees, 1843 of 1874 (98%) ward and 440 of 446 (99%) ICU patients received ≥1 antibiotic ≤24 hours after admission. Ward patients were prescribed a respiratory fluoroquinolone alone (n = 613; 33%), or beta-lactam plus macrolide (n = 365; 19%), beta-lactam alone (n = 240; 13%), among other antibiotics, including vancomycin (n = 235; 13%) or piperacillin/tazobactam (n = 157; 8%) ≤24 hours after admission. Ward patients with known risk for healthcare-associated pneumonia (HCAP), recent outpatient antibiotic use, and in-hospital antibiotic use <6 hours after admission were significantly more likely to receive nonrecommended CAP antibiotics.

Conclusions. Although more than half of ward patients received antibiotics concordant with IDSA/ATS guidelines, a number received nonrecommended CAP antibiotics, including vancomycin and piperacillin/tazobactam; risk factors for HCAP, recent outpatient antibiotic, and rapid inpatient antibiotic use contributed to this. This hypothesis-generating descriptive epidemiology analysis could help inform antibiotic stewardship efforts, reinforces the need to harmonize guidelines for CAP and HCAP, and highlights the need for improved diagnostics to better equip clinicians.

Keywords. antibiotics; community-acquired pneumonia.

Pneumonia is a leading cause of mortality and morbidity in the United States and results in substantial antibiotic usage [1–3]. Community-acquired pneumonia (CAP) is caused by a variety of pathogens, including viruses, bacteria, and fungi [4, 5]. Prior etiologic studies and clinical guidelines were based on culture and serological methods to identify bacterial and viral pathogens associated with CAP [6]. Newer diagnostics, including urine antigen detection tests and molecular methods, can more rapidly determine etiology and may be used to better guide appropriate drug selection [7–9]. However, current methods, especially those for bacterial detection, are still limited in precision, and initial antibiotic selection in most patients remains empiric [10].

In 2007, the *Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) Consensus Guidelines on the Management of Community Acquired Pneumonia in Adults* provided recommendations for empirical antibiotic therapy. They emphasized consideration of suspected etiology, pathogen-directed therapy changes, and antibiotic resistance [11]. For ward (ie, non–intensive care unit [ICU]) patients, the IDSA/ATS CAP guidelines recommended a respiratory fluoroquinolone or a beta-lactam plus a macrolide as a first-line empirical antibiotic therapy [11]. For patients admitted to the ICU, combination empirical therapy with a beta-lactam plus either azithromycin or a fluoroquinolone is recommended for patients not suspected to have *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* (MRSA) infection. For both settings, if diagnostic testing identifies an etiology, the guidelines recommended adjustment of antibiotics directed at that specific pathogen [11].

In contrast with CAP, risk factors for health-care associated pneumonia (HCAP), defined by the ATS and IDSA, included hospitalization in an acute care hospital for ≥2 days in the past 90 days; residence in a nursing home or long-term care facility;

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receipt of intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days; or attendance at a hospital or hemodialysis clinic [12]. Current first-line recommendations for the management of HCAP include early broad-spectrum antibiotic therapy to cover antibiotic-resistant pathogens [12]. Since introduction of the HCAP concept into pneumonia guidelines in 2005, new data now suggest that broad-spectrum therapy is likely not necessary for many patients meeting the HCAP criteria [13–16].

Studies using data prior to publication of the 2007 IDSA/ATS CAP guidelines suggested that clinicians appropriately used empirical antibiotic therapy for 60%–70% of hospitalized adults with CAP and adjusted therapy for <50% of patients after identifying the etiology of CAP [17–19]. However, few studies have assessed guideline-concordant antibiotic use for patients hospitalized with CAP after the 2007 IDSA/ATS guidelines were released. In this report, we assess antibiotic use among adult patients hospitalized with CAP in the ward and ICU after the introduction of these guidelines. We also assess factors associated with administration of nonrecommended CAP antibiotics among ward patients according to IDSA/ATS guidelines.

METHODS

The US Centers for Disease Control and Prevention Etiology of Pneumonia in the Community Study

The US Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) study was a prospective, multicenter, population-based, active surveillance study of patients with clinical and radiologic pneumonia from January 2010 through June 2012. Detailed EPIC study methods have been previously published [20]. In brief, investigators at study hospitals prospectively identified and enrolled eligible and consenting patients admitted with clinical and radiographic CAP. Exclusion criteria included those with recent hospitalization (within 30 days for immunocompetent or 90 days for immunocompromised patients), those who were functionally dependent nursing home or long-term care facility residents (assessed at the time of screening using the Activities of Daily Living Scale [21]), those with severe immunosuppression (see Supplementary Table 2), or those with a clear alternative diagnosis (including admission for foreign body aspiration or drug overdose). The current analysis was restricted to adults aged ≥18 years and included data from 3 hospitals in Chicago, Illinois, and 2 in Nashville, Tennessee. Public reporting of hospital adherence to the Centers for Medicare & Medicaid Services recommendations impacted clinical care [22]. However, no antibiotic stewardship programs specifically focused on the initial selection of empiric antibiotics for patients with CAP were active during the study.

Enrolled patients were interviewed using a standardized questionnaire, and medical charts were reviewed for clinical and epidemiologic information. Chest radiographs were independently reviewed by a study chest radiologist. Clinical specimens were obtained from all enrolled adult patients as soon as possible. Study-specific laboratory testing included bacterial culture, real-time polymerase chain reaction (PCR), urine antigen testing, and serology for select pathogens. Although results of diagnostic tests obtained as standard of care, including blood culture, sputum, pleural fluid, endotracheal lavage, and bronchoalveolar lavage, were available to treating clinicians, other research-specific tests were not.

Statistical Analysis

We conducted a post hoc analysis of the EPIC study using a hypothesis-generating descriptive epidemiologic design. We assessed the frequency and type of antibiotics prescribed for ward patients during the 24 hours after admission through medical record review. Prescribed antibiotics were grouped into common antibiotic classes, including aminoglycosides, beta-lactams, carbapenems, glycopeptides (vancomycin), macrolides, nonrespiratory fluoroquinolones, oxazolidinones, respiratory fluoroquinolones, or other. Among ward patients, we also described factors related to antibiotic therapy, including time to first dose; specific use of nonrecommended antibiotics such as vancomycin, linezolid, and piperacillin/tazobactam in the 24 hours after admission; ≥1 antibiotic discontinued or changed in the 72 hours after admission; and self-reported (ie, captured by interviews and medical record review) outpatient antibiotic use within 24 hours before admission.

Next, we conducted bivariate and multivariable logistic regression analysis to assess factors associated with receipt of ≥1 nonrecommended CAP antibiotic among ward patients, a patient population for which empirical therapy is clearly defined in the current IDSA/ATS guideline. Nonrecommended CAP antibiotic therapy was defined as prescribed antibiotics outside of the IDSA/ATS first-line guideline treatment recommendation of a respiratory fluoroquinolone or a beta-lactam plus a macrolide for a ward patient and is defined in detail in Supplementary Table 1. Factors determined a priori and assessed in the model included hospital, sociodemographics, underlying medical conditions, smoking, long-term care facility residence, season, clinical presentation, radiologic findings, influenza vaccination, antivirals, outpatient antibiotic use within 24 hours before admission, and inpatient antibiotic timing (Supplementary Table 2). The multivariable logistic regression model was developed using manual forward selection, considering the bivariate analysis ($P < .10$) and a conceptual framework (ie, influence of variable hierarchical interrelationships in adjustments) [23]. Age was included in the final model as prespecified age groups, and other variables were retained based on the following criterion: statistical significance, an assessment of outliers, and the Akaike Information Criterion (AIC) [24], with the smallest AIC indicating the best-fitting model. SAS version 9.3 (SAS Institute) was used for all analyses.

Because there could have been overlap between enrolled EPIC study ward patients and clinician-diagnosed HCAP, we also conducted a sensitivity analysis to assess antibiotic use excluding patients with known risk factors for HCAP. Healthcare-associated pneumonia risk factors documented in the EPIC study were immunosuppression, hemodialysis, and long-term care facility residence. We were not able to assess other HCAP risk factors, including recent intravenous antibiotic therapy, chemotherapy, wound care in the past 30 days, or hospitalization in the past 90 days, because these variables were not captured in the database. However, per the EPIC study protocol, patients with recent hospitalization (past 30 days for immunocompetent and 90 days for immunocompromised patients) were excluded.

Additionally, we reported pathogens detected among patients who received nonrecommended CAP antibiotic therapy. We described treatment received by patients specifically with MRSA or *Pseudomonas* detections.

Lastly, we described the frequency and type of antibiotics prescribed for ICU patients during the 24 hours after admission, as well as factors related to antibiotic therapy, including time to first dose; specific use of vancomycin, linezolid, and piperacillin/tazobactam in the 24 hours after admission; ≥1 antibiotic discontinued or changed in the 72 hours after admission; and self-reported outpatient antibiotic use within 24 hours before admission.

RESULTS

Analysis Among Ward Patients

Among 2320 adults enrolled in the EPIC study with clinical and radiographic CAP, 1874 (81%) were patients admitted to the ward (see Figure 1). Among the 1874 ward patients, the median length of hospital stay was 3 days (interquartile range [IQR] = 2–4), and 31 (2%) died. Within 24 hours after admission, 1843 (98%) patients received at least 1 antibiotic. Most (n = 1515, 81%) were given their first antibiotic dose within 6 hours of admission. Antibiotics prescribed within 24 hours were a respiratory fluoroquinolone alone (n = 613, 33%), a beta-lactam plus a macrolide (n = 365, 19%), a beta-lactam alone (n = 240, 13%), and a variety of other regimen combinations (n = 656, 35%) (Table 1). Specifically, 235 (13%) received vancomycin, and 157 (8%) received piperacillin/tazobactam in the 24 hours after admission. During the course of hospitalization, 958 (51%) ward patients received ≥3 antibiotics. Clinicians discontinued or changed ≥1 antibiotic during the 72 hours after admission in 1346 (72%) ward patients. Outpatient antibiotic use within 24 hours before admission was self-reported by 232 (12%) ward patients (Table 2).

Among the 1874 ward patients, 568 (30%) received nonrecommended CAP antibiotic therapy, the outcome of interest in the bivariate and multivariable models (Table 3). In the multivariable analysis, a higher odds of nonrecommended CAP antibiotic therapy was significantly associated with those at known risk for HCAP, outpatient antibiotic use within 24 hours before admission, and first antibiotic dose delivered <6 hours after admission. Patients admitted to specific hospitals, female patients, and those with asthma were less likely to have received nonrecommended CAP antibiotic therapy (Table 4). When the risk factors included in the generated "known risk for HCAP" were assessed individually in the multivariable model, long-term care facility residence, dialysis, and immunosuppression were all significant.

In the sensitivity analysis, we excluded the 674 patients with known HCAP risk factors (among whom 275 [41%] received nonrecommended CAP antibiotic therapy) and found that,

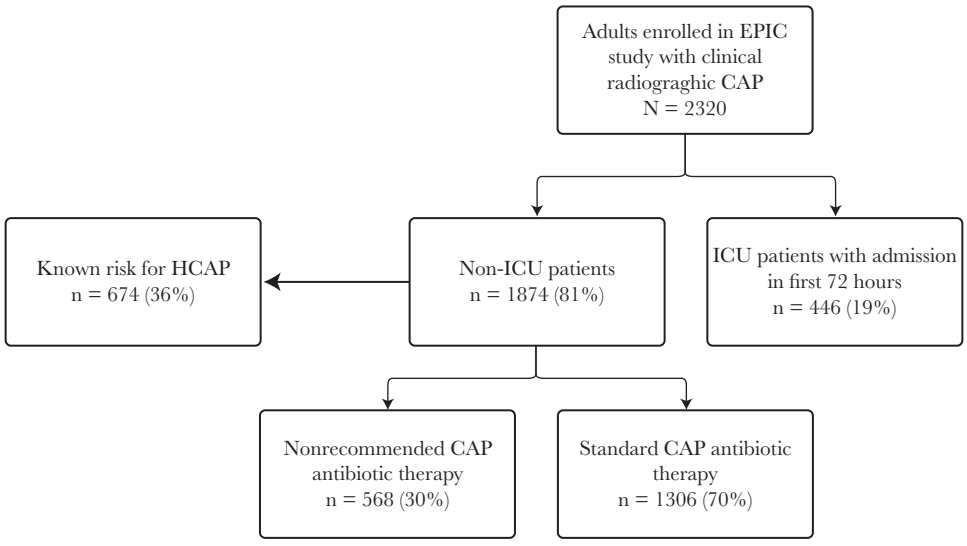

Figure 1. Flow of patients included in this analysis — Etiology of Pneumonia in the Community study, January 2010–June 2012. Abbreviations: CAP, community-acquired pneumonia; EPIC, Etiology of Pneumonia in the Community; HCAP, healthcare-associated pneumonia; ICU, intensive care unit.

Table 1. Class of Antibiotics Used in the First 24 Hours Among Ward Patients (n = 1874)

Antibiotic Class	No. (%)
Respiratory fluoroquinolone alone	613 (33)
Beta-lactam + macrolide	365 (19)
Beta-lactam alone	240 (13)
Glycopeptide alone	67 (4)
Macrolide alone	66 (4)
Respiratory fluoroquinolone + macrolide	61 (3)
Respiratory fluoroquinolone + beta-lactam	52 (3)
Respiratory fluoroquinolone + beta-lactam + macrolide	44 (2)
No therapy	31 (2)
Beta-lactam + macrolide + glycopeptide	30 (2)
Other regimen combinations[a]	328 (18)

[a]Cumulative frequency for a variety of less-common regimens (<2%)

among the remaining ward patients, 293 (24%) received nonrecommended CAP antibiotic therapy. In this multivariable analysis, first in-hospital antibiotic dose delivered <6 hours was

Table 2. Number, Timing, and Administration of Antibiotics Among Ward Patients (n = 1874)

Variable	Ward Patients (%) n = 1874
Number of antibiotics received in first 24 hours	
0	31 (2)
1	1029 (55)
2	620 (33)
3	172 (9)
4	19 (1)
5	3 (0.2)
6	0 (0)
Number of antibiotics received throughout hospitalization	
0	31 (2)
1	491 (26)
2	394 (21)
3	631 (34)
4	221 (12)
5	86 (5)
6	20 (1)
Time to first hospital antibiotic dose	
0–6 hours before admission	10 (0.5)
0–6 hours after admission	1505 (82)
7–12 hours after admission	225 (12)
>12 hours after admission	105 (6)
Vancomycin received within 24 hours after admission	235 (13)
Piperacillin/tazobactam received within 24 hours after admission	157 (8)
Linezolid received within 24 hours after admission	3 (0.2)
≥1 antibiotics discontinued or changed within 72 hours after admission	1346 (72)
Outpatient antibiotic use within 24 hours before admission	232 (12)

Table 3. Bivariate Analysis of Factors Associated With Nonrecommended Community-Acquired Pneumonia Antibiotic Therapy Among Ward Patients (n = 1874)

Factor	Nonrecommended CAP Antibiotic Therapy,[a] No. (%) n = 568	Standard CAP antibiotic therapy, No. (%) n = 1306	Crude OR (95% CI)
Site			
Hospital A	251 (44)	509 (39)	Referent
Hospital B	52 (9)	147 (11)	0.7 (0.5–1.0)
Hospital C	47 (8)	231 (18)	0.4 (0.3–0.6)
Hospital D	142 (25)	218 (17)	1.3 (1.0–1.7)
Hospital E	76 (13)	201 (15)	0.8 (0.6–1.0)
Age group			
18–49 years	164 (29)	440 (34)	0.9 (0.7–1.1)
50–64 years	183 (32)	437 (33)	Referent
65–79 years	136 (24)	267 (20)	1.2 (0.9–1.6)
≥80 years	85 (15)	162 (12)	1.3 (0.9–1.7)
Female sex	265 (47)	710 (54)	0.7 (0.6–0.9)
Race and ethnicity			
Non-Hispanic white	275 (48)	580 (45)	Referent
Black	209 (37)	543 (42)	0.8 (0.7–1.0)
Hispanic white	61 (11)	136 (10)	0.9 (0.7–1.3)
Other	23 (4)	44 (3)	1.1 (0.6–1.8)
High school education or less	228 (42)	470 (38)	0.8 (0.7–1.0)
No health insurance	64 (11)	248 (19)	1.8 (1.4–2.5)
Underlying medical conditions			
Immunosuppression	198 (35)	293 (22)	1.9 (1.5–2.3)
Chronic heart disease	196 (35)	393 (30)	1.2 (1.0–1.5)
Diabetes mellitus	143 (25)	320 (25)	1.0 (0.8–1.3)
Chronic obstructive pulmonary disease	127 (22)	269 (21)	1.1 (0.9–1.4)
Chronic kidney disease	123 (22)	153 (12)	2.1 (1.6–2.7)
Asthma	116 (20)	364 (28)	0.7 (0.5–0.8)
Neurological disorders	84 (15)	123 (9)	1.7 (1.2–2.2)
Current smoker (daily)	93 (16)	315 (24)	0.6 (0.5–0.8)
Long-term care facility resident	6 (1)	4 (0.3)	3.5 (1.0–13.6)
Known risk for health-care-associated pneumonia[b]	275 (48)	399 (31)	2.1 (1.7–2.6)

Table 3. Continued

Factor	Nonrecommended CAP Antibiotic Therapy,[a] No. (%) n = 568	Standard CAP antibiotic therapy, No. (%) n = 1306	Crude OR (95% CI)
Illness onset by season			
Winter (Dec–Feb)	163 (29)	403 (31)	0.8 (0.6–1.1)
Spring (Mar–May)	172 (31)	3557(27)	Referent
Summer (Jun–Aug)	113 (20)	237 (18)	1.0 (0.7–1.3)
Fall (Sept–Nov)	118 (21)	309 (24)	0.8 (0.6–1.0)
Clinical Presentation			
Fever	546 (96)	1249 (96)	1.1 (0.7–1.9)
Cough	480 (85)	1166 (89)	0.7 (0.5–0.9)
Fatigue	467 (82)	1022 (78)	1.3 (1.0–1.7)
Shortness of breath	437 (77)	1013 (78)	1.0 (0.8–1.2)
Chills	383 (67)	888 (68)	1.0 (0.8–1.2)
Chest pain	261 (46)	695 (53)	0.7 (0.6–0.9)
Headache	255 (45)	654 (50)	0.8 (0.7–1.0)
Myalgia	253 (45)	586 (45)	1.0 (0.8–1.2)
Nausea/vomiting	207 (36)	456 (35)	1.1 (0.9–1.3)
Diarrhea	131 (23)	260 (20)	1.2 (0.9–1.5)
Altered mental status/ confusion	114 (20)	236 (18)	1.1 (0.9–1.5)
Abdominal pain	115 (20)	264 (20)	1.0 (0.8–1.3)
Tachypnea	70 (12)	133 (10)	1.2 (0.9–1.7)
CURB-65 severity score for CAP >1[c]	174 (31)	313 (24)	1.4 (1.1–1.7)
Study radiologist findings			
Consolidation	353 (62)	814 (62)	1.0 (0.8–1.2)
Infiltrate	222 (39)	510 (39)	1.0 (0.8–1.2)
Effusion	182 (32)	352 (27)	1.3 (1.0–1.6)
Self-reported influenza vaccination	322 (58)	626 (49)	1.4 (1.2–1.8)
Antiviral treatment during hospitalization	48 (8)	83 (6)	1.4 (0.9–2.0)
Outpatient antibiotic use within 24 hours before admission	94 (17)	138 (11)	1.7 (1.3–2.2)
First hospital antibiotic dose delivered <6 hours after admission	486 (86)	1019 (78)	1.7 (1.3–2.2)

Abbreviations: CAP, community-acquired pneumonia; OR, odds ratio.

[a]This is defined in Supplementary Table 1.

[b]Immunosuppression, dialysis, and long-term care facility residents. Along with clinical signs and symptoms, this overlaps with the measurement of pneumonia severity scores.

[c]Calculated using confusion, blood urea nitrogen, respiratory rate, blood pressure, and age.

Table 4. Final Multivariable Model of Factors Associated With Nonrecommended Community-Acquired Pneumonia Antibiotic Therapy Among Ward Patients (n = 1874)

Factor	Adjusted OR[a] (95% CI)
Site	
Hospital A	Referent
Hospital B	0.7 (0.5–1.0)
Hospital C	0.5 (0.4–0.8)
Hospital D	1.3 (1.0–1.7)
Hospital E	0.8 (0.6–1.1)
Female sex	0.7 (0.6–0.9)
Known risk for healthcare-associated pneumonia[b]	2.1 (1.7–2.5)
Asthma	0.7 (0.5–0.9)
Outpatient antibiotic use within 24 hours before admission	1.6 (1.2–2.1)
First hospital antibiotic dose delivered <6 hours after admission	1.5 (1.1–1.9)

[a]Final model was adjusted for all variables in the table as well as age (determined a potential confounder a priori).

[b]Includes immunosuppression, dialysis, and long-term care facility residence. When the risk factors included in the generated "known risk for health-care associated pneumonia" were assessed individually in the multivariable model, long-term care facility residence (adjusted odds ratio [aOR] = 4.5; 95% confidence interval [CI] = 1.2–18.4), dialysis (aOR = 1.4; 95% CI = 1.2–2.4), and immunosuppression (aOR = 1.7; 95% CI = 1.4–2.1) were all significant.

still significantly associated with a higher odds of nonrecommended CAP antibiotic therapy, whereas specific hospitals and asthma continued to be significantly associated with lower odds of nonrecommended CAP antibiotic therapy. Additionally, tachypnea became significantly associated with higher odds of nonrecommended CAP antibiotic therapy.

Among the 568 ward patients who received nonrecommended CAP antibiotic therapy, 556 (98%) had etiology testing; of these, 80 (14%) had bacteria detected (including 2 patients with *Pseudomonas* and 4 with MRSA). In comparison, 1271 (97%) ward patients who received standard CAP antibiotic therapy had etiology testing; of these, 125 (10%) had bacteria detected (including 2 patients with *Pseudomonas* and 0 with MRSA). Among the 4 ward patients with *Pseudomonas*, 2 were prescribed the IDSA/ATS recommended antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin (plus 2–4 additional antibiotics in the same regimen); one received a regimen of levofloxacin alone, and the other was treated with moxifloxacin, azithromycin, and ceftriaxone. Among the 4 patients with MRSA, all received vancomycin, and 1 received linezolid added during hospitalization as recommended by IDSA/ATS for patients with MRSA.

Analysis of Intensive Care Unit Patients

Among 2320 adults enrolled in the EPIC study with clinical and radiographic CAP, 446 (19%) patients were admitted to the ICU in the first 72 hours after admission (see Figure 1), among whom 302 (68%) were admitted to the ICU on the same day as hospital admission. Among the 446 ICU patients, 440 (99%) had

≥1 antibiotic ≤24 hours after admission, and most ICU patients (n = 386, 87%) were given their first antibiotic dose <6 hours after hospital admission; 265 of 386 (88%) patients who were given their first antibiotic dose <6 hours were admitted to the ICU on the same day as hospital admission. The most common initial antibiotics prescribed among ICU patients (n = 446) were a beta-lactam plus macrolide (n = 82, 18%), a respiratory fluoroquinolone (n = 61, 14%), a beta-lactam alone (n = 42, 9%), and a large variety of other regimens (n = 261, 59%). Within 24 hours after admission, ICU patients also frequently received antibiotics with MRSA or *Pseudomonas* coverage; 175 (39%) received vancomycin, and 128 (29%) received piperacillin/tazobactam. During the entire course of hospitalization, 327 (73%) received ≥3 antibiotics. Clinicians discontinued or changed ≥1 antibiotics in the 72 hours after admission in 369 (83%) ICU patients. Outpatient antibiotic use within 24 hours before admission was self-reported by 50 (11%) ICU patients.

DISCUSSION

In our post hoc hypothesis-generating descriptive analysis of a large, prospective, observational, multisite CAP study, 52% of ward patients received a respiratory fluoroquinolone alone or a beta-lactam plus a macrolide as recommended for first-line empirical antibiotic therapy by the IDSA/ATS. However, 13% and 8% of ward patients received vancomycin and piperacillin/tazobactam in the 24 hours after admission, respectively, which are not recommended first-line empirical antibiotic therapy. Overall, one third of ward patients received nonrecommended CAP antibiotic therapy; independent factors associated with a higher odds of nonrecommended therapy were known risk for HCAP (of which long-term care residence had the strongest association), outpatient antibiotic use within 24 hours before admission, and first in-hospital antibiotic receipt <6 hours after admission, whereas specific hospitals, female sex, and asthma had lower odds of nonrecommended CAP antibiotic therapy. These findings show that clinicians prescribed broad-spectrum antibiotics for many patients with CAP even though few bacterial and resistant pathogens were detected despite extensive etiologic testing. Furthermore, following HCAP antibiotic guidelines likely led to administration of broad-spectrum antibiotics for many patients who could have been adequately treated with narrower-spectrum CAP-recommended therapy.

A range of commonly used antibiotics for inpatients with CAP have been reported in other studies, including monotherapy or combinations of beta-lactams, fluoroquinolones, and macrolides, as well as other agents such as vancomycin, doxycycline, or trimethoprim/sulfamethoxazole [19, 25–27]. A study by Berger et al using data from >100 US hospitals found that 54% of ward CAP patients from 2000 to 2009 received a fluoroquinolone or a beta-lactam plus a macrolide for initial therapy in the 24 hours after admission, which is comparable with our findings showing 52% of ward patients received these recommended IDSA/ATS regimens [28]. However, Berger et al also showed that 23% still received vancomycin (as compared with 12% in our study), and the use of vancomycin almost doubled from 2000 to 2009, which may reflect increasing concerns about MRSA infections. Similarly, Magill et al also showed that 15% of all antimicrobial drugs given to treat community-onset lower respiratory tract infections were vancomycin and piperacillin-tazobactam [3]. We also noted antibiotic therapy combinations: for example, 3% of ward patients received a respiratory fluoroquinolone plus macrolide and 18% received a range of other combinations; 2% received no therapy. This could have implications for safety risks or misdiagnosis [29]. In addition, a study by Jones et al in Department of Veterans Affairs Medical Centers from 2006 to 2010 found a substantial increase in the use of broad-spectrum antibiotics for pneumonia despite no increase in nosocomial pathogens, similar to our finding of nonrecommended antibiotic therapy despite only 10%–14% detection of bacterial pathogens among ward patients with CAP [30].

Among ward patients, several factors were associated with higher odds of nonrecommended CAP antibiotic therapy. Outpatient antibiotic use within 24 hours before admission was a significant risk factor, which suggests that clinicians likely decided that outpatient antibiotics (often oral forms) had failed. First hospital antibiotic dose delivered <6 hours after admission was also associated with nonrecommended CAP antibiotic therapy, which could be due to severely ill patients receiving broader antibiotics. Not surprisingly, known risk for HCAP, which represented 36% of our ward patients, was associated with higher odds of receiving nonrecommended CAP antibiotics. In particular, the HCAP risk factor of long-term care facility residence had the strongest association (adjusted odds ratio [aOR] = 4.5; 95% confidence interval [CI] = 1.2–18.4), despite the exclusion criteria of "functionally dependent" long-term care facility residents from the EPIC study, highlighting its role in the potential rationale for nonrecommended CAP antibiotic use. Healthcare-associated pneumonia guidelines that were in place at the time of the study recommended broad-spectrum therapy for hospitalized patients with select criteria that are thought to confer a higher risk of resistant pathogens [12]; the increased recognition of HCAP risk factors and clinicians' perception of risk may have had a strong role in the shift toward more broad-spectrum antibiotic use [30]. However, the evidence supporting HCAP recommendations for broad-spectrum antibiotic use is limited, and the definition itself is currently being revisited [13–16]. Although our sensitivity analysis showed that among patients without HCAP risk factors, 22% (n = 261/1164) received nonrecommended CAP antibiotic therapy, our database did not capture all HCAP risk factors, and thus we cannot rule out that we underestimated the role of HCAP criteria in the observed use of nonrecommended CAP antibiotics. Despite the number of patients with HCAP criteria, MRSA and *Pseudomonas* were infrequently detected in ward patients.

In contrast, certain factors were associated with decreased odds of patients receiving nonrecommended CAP antibiotics. The association with specific hospitals could suggest local differences in clinical practice from guidelines regarding antibiotic prescribing. These differences could also have been driven by varying clinical suspicion about risk factors for antibiotic-resistant infections or HCAP. A misconception that vancomycin plus an antipseudomonal beta-lactam provides better coverage for severe CAP even in ward patients who do not have known risk factors for antibiotic-resistant pathogens may have driven some treatment patterns. There was also an association with female sex, but the reasons for lower use in this group are unclear; other pneumonia studies have demonstrated varying results in relation to sex [17, 31]. Lastly, there was decreased odds in patients with asthma. Providers may perceive patients with asthma to be at lower risk for antibiotic-resistant or serious bacterial infections because viruses are often implicated in asthma exacerbations [32].

This analysis had limitations. First, study hospitals were US academic, public, and community-based institutions in urban areas, and our observations may not be representative of nonacademic hospitals or smaller, rural settings. Second, variables for influenza vaccine and outpatient antibiotic use were based on self-report and may have been subject to recall bias. In addition, prior antibiotic history was only assessed for the 24 hours before admission, and it is possible that there were additional antibiotic exposures before admission that were not evaluated and that may have influenced clinician antibiotic choices. Third, it was not possible to assess pathogen-directed changes in antibiotic therapy because reporting of diagnostic results performed for research purposes to clinicians varied among sites and by specimen type. Fourth, indications for specific antibiotic choices were not recorded, and therefore appropriateness of antibiotic selection could not be directly determined. Fifth, although the 10%–14% detection of bacterial pathogens and rare detection of *Pseudomonas* and MRSA among ward patients with CAP may suggest antibiotic overuse, current bacterial diagnostics have well-known limitations, and the need for antibiotics cannot be ruled out. Furthermore, although we confirmed CAP diagnoses by an independent review of chest radiographs, we cannot disregard the possibility of dual infectious diagnoses. Sixth, although we assessed some HCAP risk factors, we were not able to assess all HCAP risk factors because they were not systematically captured in the dataset. In particular, although immunocompromised patients with hospitalization within 90 days were excluded from the EPIC study, immunocompetent patients were only excluded if they had a hospitalization in the past 30 days. Thus, coverage for antibiotic-resistant pathogens may have been appropriate in some situations as per the HCAP guidelines [12]. Functionally-dependent long-term care facility residents were also excluded from study enrollment so we could not fully assess this HCAP risk factor, although excluding these patients should have allowed for a more restricted sample to observe true nonrecommended antibiotic use. Lastly, some regimens may have been used due to drug allergies, which were not recorded in the dataset.

Our analysis demonstrated that a substantial proportion of patients hospitalized with CAP received nonrecommended CAP antibiotic therapy. Inappropriate antibiotic selection or antibiotic overuse can jeopardize patient safety either by leading to a drug–pathogen mismatch or an increased risk of adverse events [33]. Misuse of any antibiotic is a cause for concern, but this is particularly the case for broad-spectrum drugs such as vancomycin and piperacillin/tazobactam that are important for treatment of serious healthcare-associated infections. The low incidence of *Pseudomonas*, MRSA, and other antibiotic-resistant pathogens in CAP patients without recent hospitalization, despite some HCAP risk, suggests that some use of these agents likely represents inappropriate selection. Misuse contributes to individual- and population-level antibiotic resistance to these agents, rendering them less effective for treatment of infections when needed most.

The results of this study highlight the need for updated and harmonized guidelines for CAP and HCAP, efforts that are ongoing to inform empiric antibiotic selection for CAP and antibiotic stewardship. It highlights that there is limited evidence to recommend broad-spectrum therapy for patients with HCAP risk factors, an important finding supporting the guideline harmonization efforts. Antibiotic stewardship initiatives can raise awareness of guideline-recommended treatment and promote appropriate use for CAP [34], and our results also inform stewardship considerations. To better equip clinicians with the information needed for decision making, improved diagnostics that can rule out bacterial pathogens in pneumonia or rapidly identify etiology and susceptibility of the bacterial pathogen causing pneumonia are urgently needed. Until improved diagnostics are developed to accurately and rapidly identify etiologies, therapy should be guideline driven according to clear CAP and HCAP recommendations.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. E. J. A. has received funding from MedImmune for ongoing clinical trial work and other studies and has also served as a consultant for Abbvie for respiratory syncytial virus. All other authors report no potential conflicts.

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