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Ceftaroline Fosamil for Treatment of Methicillin-Resistant *Staphylococcus aureus* Hospital-Acquired Pneumonia and Health Care–Associated Pneumonia

A 5-Year Matched Case-Control Evaluation of Epidemiology and Outcomes

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Purpose: Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia patients treated with current antibiotic therapies have exhibited poor outcomes, increased hospital length of stay, and higher costs of care. Twenty-eight-day mortality rate of 32% was reported with vancomycin therapy for MRSA hospital-acquired pneumonia (HAP) and MRSA health care–associated pneumonia (HCAP) from the same institution. The purpose of this study was to compare the epidemiology and effectiveness of ceftaroline versus alternative antibiotic therapies: linezolid, vancomycin, and/or cefepime, in hospitalized patients with MRSA HAP or HCAP based on clinical outcomes.

Methods: Through retrospective matched case-control study design, the Infectious Diseases Society of America– and Centers for Disease Control and Prevention–defined MRSA HCAP or HAP consecutive hospitalized subjects treated with either ceftaroline fosamil (CPT-F) or alternative antibiotics were compared. Primary outcomes were 28-day mortality and 14-day clinical evaluation. Secondary outcomes included duration of hospitalization, complications with treatment, and clinical response to therapy switches.

Results: Overall, 40 cases of MRSA HAP or HCAP treated with CPT-F were matched to 109 control subjects treated with either vancomycin or linezolid based on age, intensive care unit status, and type of pneumonia infection. The CPT-F cohort had a 10% (n = 4) 28-day mortality rate, and 91% (n = 32) had 14-day clinical success/cure (±1 day) from diagnosis of pneumonia for the 35 evaluable cases. Of the 4 patients who died, 3 had debilitating comorbid conditions and an overall APACHE (Acute Physiology and Chronic Health Evaluation) II score greater than 20. Of those failing on standard antibiotic therapy, 50% (n = 20) were switched to CPT-F; subsequently, all (n = 20) switched patients cleared pneumonia. The overall success rate with CPT-F was 90% versus 75% for comparators.

Conclusions: Treatment of MRSA pneumonia with CPT-F is associated with overall lower 28-day mortality than earlier studies with other agents. These data suggest a possible benefit in the use of CPT-F for therapy of MRSA hospital-acquired and health care–associated pneumonia.

Key Words: ceftaroline fosamil, health care–associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), methicillin-resistant *Staphylococcus aureus* (MRSA)

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of health care–associated pneumonia (HCAP) with high rates of morbidity and mortality. Strains with reduced susceptibility to vancomycin have limited treatment options, with these infections having been shown in some reports to have documented inferiority with vancomycin in comparison to β-lactam antibiotics.[1] Its prevalence in HCAP and hospital-acquired pneumonia (HAP) along with risks for acquisition and optimal measures for management remain uncertain. The emergence of new strains, rise in antibiotic resistance, and frequently documented outbreaks of severe pneumonia among healthy persons has further complicated management of MRSA pneumonia.[2–4] In addition, MRSA pneumonia patients treated with current antibiotic therapies have exhibited poor outcomes, increased hospital length of stay (LOS), and pose a burden on the health system with high costs for care, in particular because of readmissions.[5,6]

Ceftaroline is a broad-spectrum β-lactam antibiotic that was approved by the Food and Drug Administration in 2010 for treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. It displays potent in vitro activity against MRSA strains and other resistant pathogens[7]; however, it is not Food and Drug Administration approved for the treatment of MRSA HAP and HCAP. The CAPTURE (Clinical Assessment Program and TEFLARO Utilization Registry) phase 3 studies have reported an overall clinical success rate of 84.3% achieved with ceftaroline in CAP subjects.[8] Our study's main objective was to establish the noninferiority of the clinical cure rate of ceftaroline compared with that of vancomycin and other standard therapies for the off-label treatment of MRSA HAP and HCAP. We hypothesized that ceftaroline has comparable efficacy and can be used safely as rescue therapy in the treatment of MRSA HAP and HCAP.

METHODS

A comparative retrospective matched case-control study was conducted utilizing the American Thoracic Society/Infectious Diseases Society of America definitions for HAP and HCAP. All treatment agents are commonly used at Henry Ford Hospital, a 900-bed teaching acute care hospital in Detroit, Mich. The objective of this study was to compare the epidemiology and

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effectiveness of ceftaroline versus alternative antibiotic therapies: linezolid, vancomycin, and/or cefepime, in hospitalized patients with MRSA HAP or HCAP based on defined clinical outcomes. The primary outcome was clinical cure or the recurrence of infection at 14 and 28 days from onset of infection, and secondary outcomes included duration of hospitalization, complications with treatment, and duration of therapy. Success was defined as either cured, with complete resolution of signs and symptoms of pneumonia infection, or an improvement with partial resolution of signs and symptoms of infection. Failure was progression of baseline signs and symptoms of pneumonia with or without change in antibiotics, specifically deterioration with change in antibiotics, relapse of infection, or death.

Initial identification of subjects with the infections was through Theradoc, an electronic information system. Predefined patient characteristics and outcomes, including complete demographic information, risk factors for MRSA, treatments, and clinical and laboratory characteristics for all study subjects, were abstracted from CarePlus, an electronic medical records database, and entered into a study-specific catalog utilizing a standardized case report form. Adverse effects and toxicity from the antibiotics in this study population including nephrotoxicity and respiratory and infectious complications were assessed in both treatment groups, as well as differences within the 2 study groups by effectiveness of treatment, duration of antibiotic therapy, and relapse of infection. Importantly, improvement in a patient's clinical course within the first 72 hours from treatment initiation was also recorded. An early clinical response to treatment within 72 hours from admission was on the basis of absence of the following symptoms: fever (≥38°C), leukocytosis, O_2 requirement, cough, and chest pain. If 2 of the 3 symptoms (fever [≥38°C], leukocytosis, and/or O_2 requirement) did not persist within the first 72 hours, the patient was considered to have exhibited an early response to treatment. The initial identification of isolates and susceptibility testing via Vitek 2 (BioMérieux, Inc, Durham, NC) was performed by the clinical microbiology laboratory. The minimum inhibitory concentration (MIC) for ceftaroline, vancomycin, and linezolid were performed on all isolates utilizing Epsilometer tests (E-test; BioMérieux, Inc) according to the manufacturer's instructions. The MICs for vancomycin were also performed on all isolates using broth microdilution according to the Clinical and Laboratory Standards Institute guidelines.[9] Detection for vancomycin heteroresistance was performed using macrodilution method E-test (BioMérieux, Inc) according to the manufacturer on brain-heart infusion agar (BBL; Becton Dickinson, Cockeysville, Md). The plates were incubated at 35°C in ambient air, and results are read at 24 and 48 hours. A strain was determined to have heteroresistance if vancomycin and teicoplanin MIC was 8 mg/L or greater or teicoplanin MIC was 12 mg/L or greater.[10]

Inclusion/Exclusion

Hospitalized subjects were included from January 2009 to May 2013 and matched based on 3 criteria: (1) age (<65 or ≥65 years), (2) intensive care unit (ICU) status, and (3) type of pneumonia, HCAP or HAP. Patients younger than 18 years, those who were treated with the antibiotic of interest for less than 48 hours, with incomplete medical records, and those who were transferred to another facility or had an unevaluable outcome at day 28 from initial diagnosis of infection were excluded from this study.

Sample Size and Statistical Analysis

We estimated a sample size collection of charts on a total of 160 patients who were hospitalized with MRSA pneumonia, with approximately 40 patients (25%) treated with ceftaroline and 120 patients (75%) treated with other therapeutic agents; patients treated with ceftaroline versus other agents were matched 1:3 to yield a sufficient sample size for comparative analysis, using 2-sided significance level for α of 0.05 and 80% power.

At the completion of data collection, a multivariate analysis was conducted to determine risk factors and independent variables associated with outcomes in the patients to be studied. Categorical variables were compared using a χ^2 test or Fisher exact test where sample sizes are small. Continuous variables were compared using the 2-sample *t* test. $P < 0.05$ was considered statistically significant. Data were analyzed using both SPSS software version 20 (IBM Corporation, Armonk, NY) and SAS software version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

Cases

Overall, 40 consecutive cases of MRSA pneumonia treated with ceftaroline fosamil (CPT-F) monotherapy were identified from July 2011 to April 2013. The average duration of therapy with ceftaroline was 12.4 days with median dosage of 600 mg/kg (range, 200–600 mg/kg). Twenty-seven cases were HCAP, and 13 cases were HAP. Mean age was 58.8 (SD, 16.1) years; 50% were females, 42% were African American, and mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 15 (SD, 6.8). Vancomycin MIC90 was 1.5 μg/mL by E-test, mean MIC for CPT-F was 0.56 μg/mL, and mean MIC for linezolid was 1.22 μg/mL. Mean hospital LOS was 27.7 days. Twenty percent of cases (n = 8) were hospitalized for 5 days or more before antibiotic therapy for MRSA pneumonia was started. Forty-six percent of HAP cases were hospitalized for 2 or more days within the prior 90 days before antibiotics for HAP were started, current hospitalization excluded. In addition, 1 case was clinically diagnosed with bronchiectasis, but completed CPT-F therapy successfully. The primary 14-day clinical outcome (±1 day) from diagnosis of pneumonia for the 35 evaluable cases was 91% (n = 32) success/cure of infection, 2 patients were considered treatment failures, and 1 patient died. The overall 28-day mortality was observed in 10% (n = 4) of the total population. Of the 4 control patients who died, 3 had debilitating comorbid conditions and an overall APACHE II score greater than 18. Fifty percent (n = 20) of cases were considered switch patients, as they were initially started on standard antibiotic therapy (ie, vancomycin and/or cefepime, linezolid) but failed initial therapy and were switched to CPT-F; consequently, all 20 patients had success by end of treatment. The average length of therapy was 7 days before being switched to CPT-F. Seven cases (17.5%) demonstrated an early clinical response to treatment with CPT-F within 72 hours from admission. In addition, only 1 patient reported an allergy to CPT-F and was discontinued; for this reason, that patient was excluded from the total cohort of cases. Overall, CPT-F was well tolerated by all patients, and no major complications were reported (Table 1).

Control Subjects

One hundred nine MRSA pneumonia subjects were identified from January 2009 to May 2013 and matched to the 40 cases by age (>65 or ≥65 years), type of pneumonia, and ICU positive status. Seventy-five control subjects were HCAP, and 34 control subjects were HAP. Mean age was 58.8 (SD, 16.4)years, 50% were males, 46% were African American, and mean APACHE II score was 13 (SD, 6.7). Intensive care unit positive status at onset of pneumonia was seen in 62% of control subjects. The mean hospital LOS was 23.4 days. Eighty-seven percent (n = 95) of control subjects were treated with vancomycin alone, or in conjunction

TABLE 1. Univariate Analysis of Patient Demographics, Characteristics, and Clinical Outcome by Antibiotic

Variable	Ceftaroline-Treated Cases (n = 40)	Controls Treated With Other Agents (n = 109)	*P*
Type of pneumonia			0.879
HCAP	27 (67.5%)	75 (69%)	
HAP	13 (32.5)	34 (31.2%)	
Age, mean (SD), y	58.8 (16.1)	58.8 (16.4)	1.00
Sex, male, n (%)	20 (50%)	54 (50%)	0.960
Race- African American, n (%)	16 (42%)	46 (50%)	0.957
APACHE II score, mean (SD)	15 (6.8)	13 (6.7)	0.1099
Total hospital LOS, mean (SD)	27.7 (24.4)	23.4 (19)	0.260
Previous use of antibiotics 30-d prior to pneumonia onset, n (%)	4 (11.8%)	24 (23.3%)	0.1538
ICU at onset of pneumonia, n (%)	22 (55%)	68 (62.4%)	0.530
Cancer, n (%)	10 (25%)	16 (14.8%)	0.219
Human immunodeficiency, n (%)	2 (5%)	1 (1%)	0.176
Diabetes mellitus, n (%)	10 (25%)	20 (19%)	0.505
Liver disease, n (%)	8 (20%)	9 (8.3%)	0.088
IVDU, n (%)	3 (7.5%)	9 (8.4%)	1.00
Dialysis (HD or PD), n (%)	1 (2.5%)	3 (2.8%)	1.00
Congestive heart failure, n (%)	8 (20%)	22 (20.4%)	0.980
Vascular disease, n (%)	2 (5%)	7 (6.5%)	1.00
Chronic obstructive pulmonary disease, n (%)	8 (20%)	31 (29%)	0.408
Clinical Outcome	**CPT-F (n = 40)**	**Non-CPT-F Treated (n = 109)**	***P***
28-d Mortality (±3 d from diagnosis of pneumonia), n (%)	4 (10%)	16 (14.7%)	0.5922

IVDU indicates intravenous drug user.

with cefepime, 51% (n = 56), and 36% (n = 39) were treated with linezolid. Overall, 28-day mortality was observed in 14.7% (n = 16); 14-day clinical success/cure rate was 87% (n = 75) of the 86 evaluable control subjects, with n = 5 deaths and 6 patients considered failures. Of the control subjects who had 28-day mortality, 12 (75%) were on vancomycin in conjunction with cefepime, 3 patients were on linezolid, and 1 control subject was on vancomycin monotherapy. The attributable mortalities for all 16 patients were due to infection not clearing or causing further complications, which eventually led to death. Of the 109 control subjects, 1 patient isolate with a respiratory source was vancomycin heteroresistant, with a corresponding vancomycin MIC by E-test for this isolate of 3.0 μg/mL. The mean MIC by E-test for vancomycin was 1.5 μg/mL; the mean MIC for ceftaroline and linezolid by E-test was 0.75 μg/mL. In addition, all isolates (n = 107) were taken from a respiratory source, with the exception of 2 isolates, which were taken from a blood source.

Comparative Analysis

A univariate logistic regression analysis (with each study variable analyzed separately) is presented in Table 2, and the multivariable logistic regression results (with the potentially influential study variables analyzed together) are presented in Table 3. Potentially influential study variables used in the multivariable modeling were defined as those with univariable $P < 0.20$. Conditional logistic regression modeling was used throughout to account for the case-control matching. The outcome of interest was defined as mortality at 28 days. The human immunodeficiency and dialysis variables could not be analyzed because none of the mortality patients had either of those conditions. The results indicate that the CPT-F patients were not significantly associated (either univariably or multivariably) with the mortality outcome of interest. However, the multivariable result approached significance, with the odds ratio of less than 1 indicating that CPT-F was almost protective against mortality. Logistic regression also

TABLE 2. Univariable Logistic Regression Results for Mortality at 28 Days Using Conditional Regression Modeling to Account for the Case-Control Matching

Variable	*P*	Odds Ratio	Odds Ratio 95% Confidence Limits	
Ceftaroline treatment	0.495	0.679	0.223	2.064
HCAP pneumonia	0.718	0.833	0.308	2.248
Age	0.939	1.002	0.943	1.065
Male sex	0.966	0.978	0.359	2.665
African American race	0.385	1.609	0.551	4.696
APACHE II	0.209	1.052	0.972	1.139
Total LOS	0.427	0.987	0.956	1.019
Previous antibiotics	0.301	1.947	0.551	6.886
ICU at onset of pneumonia	0.144	0.167	0.015	1.838
Cancer	0.014*	4.623	1.368	15.623
Diabetes	0.637	1.336	0.402	4.437
Liver disease	0.199	3.119	0.551	17.665
IVDU	0.345	2.193	0.430	11.194
Congestive heart failure	0.202	0.398	0.097	1.640
Peripheral vascular disease	0.719	0.654	0.065	6.603
Chronic obstructive pulmonary disease	0.127	2.523	0.770	8.273

*Statistically significant, $P < 0.05$.

IVDU indicates intravenous drug user.

TABLE 3. Multivariable Regression Results for Mortality at 28 Days Using Conditional Regression Modeling to Account for the Case-Control Matching

Variable	*P*	Odds Ratio	Odds Ratio 95% Confidence Limits	
Ceftaroline treatment	0.085	0.207	0.034	1.245
ICU at onset of pneumonia	0.395	0.141	0.002	12.843
Cancer	0.008*	12.352	1.902	80.202
Liver disease	0.046*	14.020	1.053	186.669
Chronic obstructive pulmonary disease	0.757	0.799	0.193	3.312

Variables with univariable $P < 0.20$ have been included, along those in ceftaroline treatment.

*Statistically significant, $P < 0.05$.

confirmed the association between ceftaroline treatment and decreased risk of clinical failure (adjusted odds ratio, 0.207; 95% confidence interval, 0.034–1.245). The basic data breakdown indicates that the mortality outcome was seen in 4 of 40 ceftaroline-treated patients (10.0%) and 16 of 109 comparator-treated patients (14.7%). The difference between those 2 percentages was not statistically significant (χ^2 $P = 0.425$).

DISCUSSION

Overall, ceftaroline was well tolerated by all patients. The success rate with ceftaroline was 90% versus 75% for comparators at day 28 from diagnosis of pneumonia. This study did not identify any significant differences between ceftaroline and other comparator agents with respect to mortality, development of complications of therapy or nephrotoxicity, mechanical ventilator days, or length of ICU or hospital stay. Patients with MRSA HCAP or HAP who were treated with ceftaroline were more likely to reach clinical success when compared with vancomycin- and/or other treatment regimen–treated patients. Earlier studies have shown superior success rates with linezolid in comparison to vancomycin in a prospective, double-blind trial.[11,12] The clinical success rate of 90% observed among ceftaroline-treated patients in our study is high compared with success rates reported in previous studies.[13,14] There are several possible explanations for the relatively low mortality rate for both cases and control subjects in this study: primarily that we studied patients with HCAP or HAP in contrast to ventilator associated pneumonia (VAP). The low mortality rate found in this study limits the power to detect any statistical or clinical differences in mortality between treatment groups. Moreover, because it has been suggested that the attributable mortality of VAP is less than 10%,[15] the statistical power to detect differences in VAP-related mortality is even lower. The attributable mortalities for all 4 ceftaroline-treated patients who died were due to complications unrelated to MRSA pneumonia infection. Albeit 50% of cases utilized ceftaroline as a second line of therapy citing disease progression as the reason for switch, all switched patients experienced clearance of infection by end of treatment. Thus, ceftaroline proves to be effective for positively impacting patient outcomes in subjects requiring a change in their prior antibiotic regimen or those with comorbidities that are not well tolerated by vancomycin.

In our study, clinical pharmacists were actively involved in the dosing and management of vancomycin. Suboptimal trough levels in vancomycin-treated patients were not a factor in the present study, as all patients had recommended vancomycin trough levels of 15 to 20 μg/mL. An earlier publication from Haque et al[2] reported that mortality among patients with MRSA HCAP, HAP, and VAP increased as a function of vancomycin MIC. Of the 111 patients in the current study for whom vancomycin MICs were available, the majority (94%) had vancomycin MICs of greater than 1 μg/mL, which may explain the lower success rates seen in the vancomycin group.

Finally, in this study, we found ceftaroline to be as effective as compared with linezolid and vancomycin for the treatment of MRSA HCAP and HAP. It also has been hypothesized that the better lung penetration of linezolid may in part explain the improved outcomes seen in patients with MRSA VAP.[16] The same hypothesis may be the case for ceftaroline, or its bactericidal activity may play a role. However, our study cannot address these hypotheses. Our study has several limitations. First, this study was observational in design, which has inherent limitations. Second, the HCAP and HAP diagnosis was based on Centers for Disease Control and Prevention surveillance criteria, which may misclassify some cases. Third, the study was single center and nonrandomized. The primary strength of our study is that we had limited exclusion criteria, and all case patients were conditionally matched to control subjects based on factors previously shown to be associated with mortality (age, ICU status, and type of pneumonia infection). Thus, our results are more generalizable to clinical practice settings.

Furthermore, the findings of this study indicate that ICU admissions, liver disease, and cancer status are frequent events in the patients we studied, and there were statistically significant differences in the incidence of the latter 2 characteristics in patients we followed up who were treated with ceftaroline versus linezolid or vancomycin. The renal deterioration seen in patients with MRSA HCAP and HAP appears independent of antibiotic choice and may be caused by other conditions common in the critically ill.

We found no difference in resource utilization between patients with MRSA HCAP or HAP in terms of length of hospitalization. To develop interventions to control resource utilization and the cost of care among patients with HCAP and HAP, factors beyond appropriate antibiotic therapy should be explored. In conclusion, this study adds to the evidence indicating that patients with MRSA HCAP and HAP who are treated with CPT-F are likely to respond favorably and as effectively as did patients treated with vancomycin or linezolid. These results suggest that ceftaroline should be considered as an effective treatment option for patients with MRSA HCAP or HAP, especially in those patients with high MICs and renal insufficiencies.

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