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CLINICAL THERAPEUTICS

Randomized Noninferiority Trial of Cefoperazone-Sulbactam versus Cefepime in the Treatment of Hospital-Acquired and Healthcare-Associated Pneumonia

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ABSTRACT Cefoperazone, a third-generation cephamycin with broad-spectrum antibacterial activity and the ability to permeate bacterial cell membranes, is active against commonly encountered multidrug-resistant pathogens for hospital-acquired pneumonia (HAP) and health care-associated pneumonia (HCAP). To clarify the clinical effects of cefoperazone-sulbactam in the treatment of HAP and HCAP, we conducted an open-label, randomized, noninferiority trial that recruited patients aged ≥18 years suffering HAP/HCAP. Participants were randomly assigned to the cefoperazone-sulbactam (2 g of each per 12 h) or cefepime (2 g per 12 h) arm. Clinical and microbiological responses were evaluated at early posttherapy and test-of-cure visits. Recruited patients were allocated to subpopulations for intent-to-treat ($n = 154$), per-protocol ($n = 147$), and safety ($n = 166$) analyses. Intent-to-treat analysis demonstrated that (i) at the early posttherapy visit, 87.3% of patients receiving cefoperazone-sulbactam and 84.3% of patients receiving cefepime achieved clinical improvement or cure (risk difference of 3.0%; 95% confidence interval [CI], −9.0% to 15.0%), and (ii) at the test-of-cure visit, 73.1% of patients receiving cefoperazone-sulbactam and 56.8% of patients receiving cefepime were assessed as cured (risk difference of 16.3%; 95% CI, 0.0% to 33.0%). These results indicated the noninferiority of cefoperazone-sulbactam to cefepime, which was confirmed by per-protocol analysis. The chest radiographic consolidation/infiltration resolution rate, microbiological eradiation rate, and percentage of adverse events were comparable in both groups. Serious adverse events were rare, and none was judged to be related to the study

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drugs. Cefoperazone-sulbactam at 2 g every 12 h was noninferior to cefepime at 2 g every 2 h for patients with HCAP.

KEYWORDS cefoperazone-sulbactam, cefepime, healthcare-associated pneumonia, hospital-acquired pneumonia, noninferiority trial

Pneumonia has been one of the leading causes of morbidity and mortality (1). Early diagnosis of pneumonia for starting antibiotic therapy is very important (2), and this is especially true for hospital-acquired pneumonia (HAP) and health care-associated pneumonia (HCAP), as they often involve vulnerable patients who are elderly and/or have multiple comorbidities (1–3). The earlier an appropriate antibiotic therapy is started, the better the outcome of the pneumonia (2). However, etiologies of pneumonia are not always clearly identifiable (1–4), and pathogens are often multidrug resistant (MDR) in the case of HAP (1, 5) and in substantial number of HCAP cases in some geographic locales, including Taiwan (6, 7). Given the progressively aging population in Taiwan (8), increasing numbers of elderly patients with multiple comorbidities are released from hospitals to long-term care facilities after completing medical treatment, and the aging-inherent vulnerability makes them subject to high chances of repetitive bacterial infections, including pneumonia, causing them to seek medical help (7, 9). Under these circumstances, the line between HCAP and HAP in terms of etiologies is often blurred (7, 9, 10). Among the potential etiologies, Gram-negative bacilli (GNB) play important roles in developing HAP and HCAP. *Enterobacteriaceae* members, *Pseudomonas aeruginosa*, and other non-glucose-fermenting Gram-negative bacilli are often presumed to be culprit pathogens for HAP and HCAP and, therefore, are targets for coverage by empirical antibiotic(s) (1). Based on the etiology presumption and facility/region epidemiological data of antibiotic resistance, a limited number of antibiotics with intrinsic antipseudomonal effects, such as ceftazidime, cefepime, and group 2 carbapenems, are usually recommended for empirical treatment for HAP and HCAP (1). Given the fact of progressive global increase in MDR bacterial isolates and the discovery of new antibiotics lagging behind the demand for the coverage of emerging MDR microbes (11, 12), any antibiotic, regardless of whether it is a new or old one, that potentially effectively treats infections due to MDR bacteria should be highly valued.

Cefoperazone, a third-generation cephamycin with broad-spectrum antibacterial activity and the ability to permeate bacterial cell membranes, is active against *Enterobacteriaceae* members, *P. aeruginosa*, and other non-glucose-fermenting Gram-negative bacilli, as well as anaerobes in general (13, 14); it was documented that cefoperazone's antibacterial strength is markedly augmented by combination with sulbactam (15–18). However, data regarding clinical effects of cefoperazone-sulbactam in the treatment of HAP and HCAP are largely lacking. To clarify this information, a randomized noninferiority trial was conducted to compare the efficacy and safety of cefoperazone-sulbactam versus cefepime in the treatment of patients with HAP and HCAP.

RESULTS

Participant flow and recruitment. Of a total of 174 subjects screened, 168 subjects fulfilled the recruitment criteria, accepted the invitation to participate in this study, and underwent randomization. Two patients withdrew their consents before starting the trial; 166 patients received the study drugs. Eventually, 154 patients were included for intent-to-treat (ITT), 147 for per-protocol (PP), and 166 for safety analyses. The study groups and exclusion events are summarized in Fig. 1. Of note, recruitment was discontinued after inclusion and random allocation of 166 patients because the number of patients for PP analysis had already exceeded the estimated numbers needed to be fully evaluated in this study with slow recruitment spanning 3 years.

Baseline data and antibiotic treatment durations. Similar baseline characteristics were found in both study groups, except for the higher mean body mass index (21.4 ± 3.6 versus 20.1 ± 3.6 kg/m^2; $P = 0.048$) being found in patients in the cefepime arm. Most of the included patients were elderly (mean age, 77.6 ± 12.5 years) and had

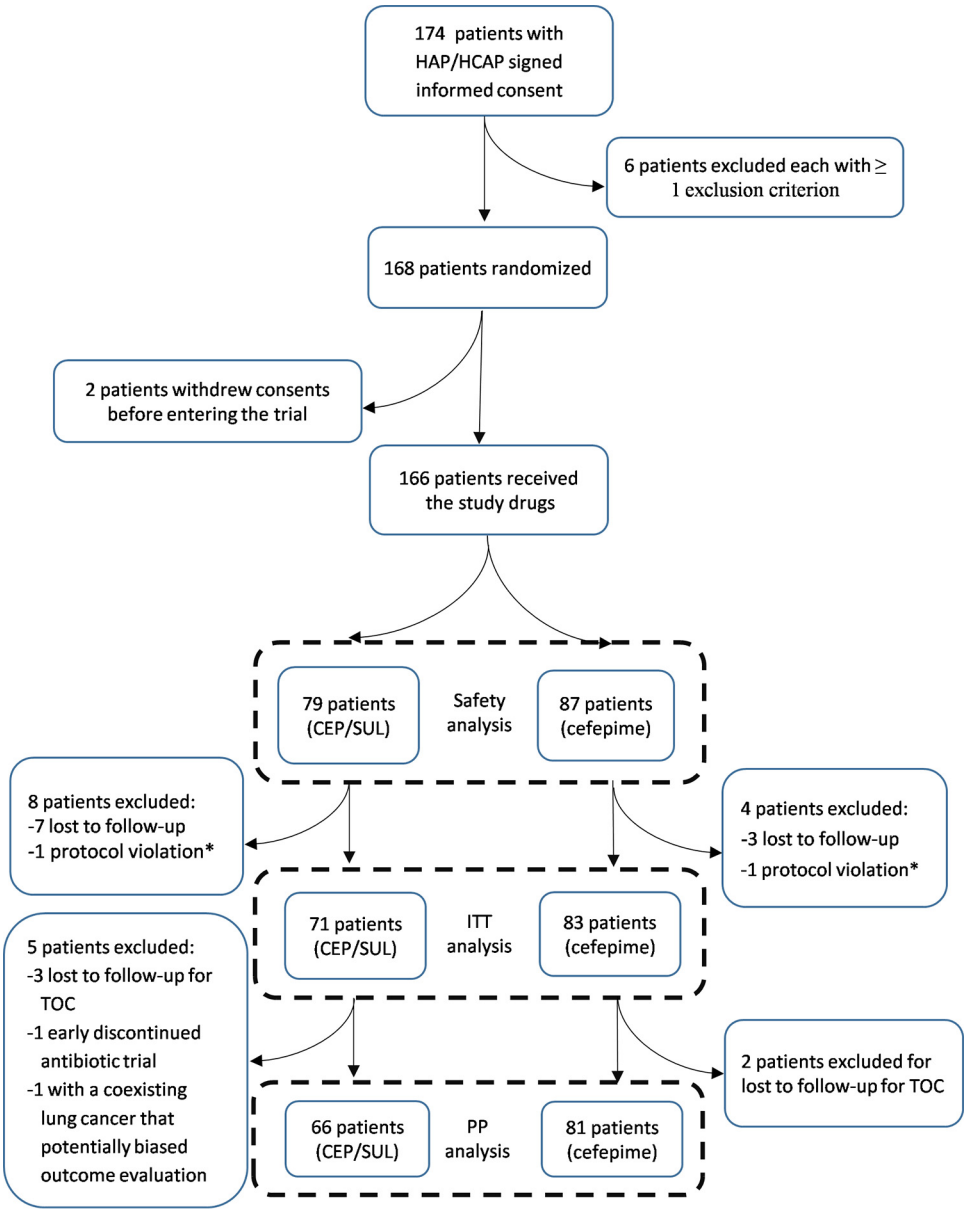

FIG 1 Trial profile. HAP/HCAP, hospital-acquired pneumonia/health care-associated pneumonia; CEP/SUL, cefoperazone-sulbactam; TOC, test of cure. Asterisks indicate patient inclusion and conducting of the antibiotic trial at a branch hospital rather than the center that was registered as the study site.

multiple comorbidities. Baseline data are detailed in Table 1. There was no significant difference between the antibiotic treatment durations in the two arms (Table 2).

Clinical responses. In the ITT analysis, we found that (i) at the early posttherapy (EPT) visit, 62/71 (87.3%) patients receiving cefoperazone-sulbactam and 70/83 (84.3%) patients receiving cefepime achieved clinical success (cure or improvement) (difference in success rate, 3.0%; 95% confidence interval [CI], −9.0% to 15.0%), demonstrating the noninferiority of cefoperazone-sulbactam to cefepime, and (ii) at the test-of-care (TOC) visit, 49/67 (73.1%) patients receiving cefoperazone-sulbactam and 46/81 (56.8%) patients receiving cefepime were assessed as cured (difference in cure rate, 16.3%; 95% CI, 0.0% to 33.0%), again demonstrating the noninferiority of cefoperazone-sulbactam to cefepime (Table 3).

The PP analysis confirmed the noninferiority of cefoperazone-sulbactam to cefepime, where (i) 54/66 (81.8%) patients receiving cefoperazone-sulbactam and 64/81 (79.0%)

TABLE 1 Baseline characteristics of patients who underwent treatment assignments (ITT population)

Characteristic[c]	Treatment arm			
	Overall assignment (*N* = 154)	Cefoperazone-sulbactam (*N* = 71)	Cefepime (*N* = 83)	*P* value[a]
Male, *n* (%)	117 (76.0)	56 (78.9)	61 (73.5)	0.316
Age (yr), mean ± SD	77.6 ± 12.5	76.9 ± 13.5	78.2 ± 11.6	0.468
Weight (kg), mean ± SD	54.5 ± 11.5	53.4 ± 11.3	55.4 ± 11.6	0.225
Body mass index (kg/m^2), mean ± SD	20.8 ± 4.2	20.1 ± 3.6	21.4 ± 4.6	0.048
Blood culture positive for bacterial growth, *n* (%)	15 (9.7)	7 (9.9)	8 (9.6)	0.193
Sputum culture positive for bacterial growth, *n* (%)	56 (36.4)	27 (38.0)	29 (34.9)	0.423
Comorbidity,[b] *n* (%)				
Hypertension	113 (73.4)	52 (73.2)	61 (73.5)	>0.999
Diabetes mellitus	53 (34.4)	22 (31.0)	31 (37.3)	0.497
COPD	39 (25.3)	20 (28.2)	19 (22.9)	0.464
Prior stroke	29 (18.8)	18 (25.4)	11 (13.3)	0.065
CHF	24 (15.6)	11 (15.5)	13 (15.7)	>0.999
Parkinsonism	22 (14.3)	10 (14.1)	12 (14.5)	>0.999
CKD	14 (9.1)	4 (5.6)	10 (12.0)	0.261
Peptic ulcer, *n* (%)	18 (11.7)	10 (14.1)	8 (9.6)	0.455

[a]For comparisons between the cefoperazone-sulbactam and cefepime arms.
[b]Individual patients might have more than one comorbidity.
[c]COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CKD, chronic kidney diseases. Percentages refer to $n/N \times 100$.

patients receiving cefepime achieved clinical success (difference in success rate, 2.8%; 95% CI, −11.4% to 17.0%), and (ii) 49/66 (74.2%) patients receiving cefoperazone-sulbactam and 46/81 (56.8%) patients receiving cefepime were assessed as cured (difference in cure rate, 17.4%; 95% CI, 1.0% to 34.0%). Evaluation of the clinical responses in ITT and PP analyses by the investigators was in agreement with those of the blinded evaluator.

There were no significant differences between the cefoperazone-sulbactam and cefepime groups regarding the chest radiographic improvement (complete and partial resolution of lung consolidation/infiltration) rates found at the EPT ($P = 0.592$) and TOC ($P = 0.510$) assessments. Improvement rates in both arms were found to increase over time from EPT to TOC visits.

In total, 16 bacterial isolates grew from the culture of good-quality sputum specimens obtained from 14 recruited patients. *P. aeruginosa* isolates ($n = 8$ [8/16; 50.0%]) were most frequently found, followed by *Haemophilus influenzae* ($n = 2$) and one isolate for each of the other bacterial species. All bacterial isolates were susceptible to the study drugs *in vitro*. Four patients suffering from pneumonia, with *P. aeruginosa* isolated from sputum, were allocated in the cefoperazone-sulbactam arm, while another 4 were in the cefepime arm; all of these patients were HCAP cases. Of note, an *A. baumannii* isolate was found to grow concurrently from the sputum of 1 of the 4 patients in the cefoperazone-sulbactam arm, and one patient in the cefepime arm died. Clinical success rates in patients suffering pneumonia due to *P. aeruginosa* in the

TABLE 2 Treatment durations in different treatment arms

Antibiotic treatment duration	No. (%) of patients assessed as clinical success (cure or improvement) at TOC visit[a]			
	Overall included	Cefoperazone-sulbactam arm	Cefepime arm	*P* value[b]
ITT analysis				
7–14 days	114 (95.8)	55 (100)	59 (92.2)	0.186
15–21 days	5 (4.2)	0 (0.0)	5 (7.8)	0.061
PP analysis				
7–14 days	113 (95.8)	54 (100)	59 (92.2)	0.159
15–21 days	5 (4.2)	0 (0.0)	5 (7.8)	0.062

[a]Percentages refer to $n/N \times 100$. Mean (±SD) number of days of treatment for the ITT analysis were the following: overall, 10.3 ± 2.9 (119 patients); cefoperazone-sulbactam arm, 9.9 ± 2.8 (55 patients); cefipime arm, 10.6 ± 3.0 (64 patients). Mean (±SD) number of days of treatment for the PP analysis were the following: overall, 10.2 ± 2.9 (118 patients); cefoperazone-sulbactam arm, 9.9 ± 2.8 (54 patients); cefepime arm, 10.6 ± 3.0 (64 patients).
[b]For comparisons between the cefoperazone-sulbactam and cefepime arms.

TABLE 3 Clinical response rates at EPT/TOC visits

Clinical response	Cefoperazone-sulbactam[a]	Cefepime[a]	Risk difference[b] (%)	95% CI
ITT analysis				
EPT visit, *N*	71	83		
Cured or improved, *n* (%)	62 (87.3)	70 (84.3)	3.0	−0.09 to 0.15
TOC visit, *N*	67	81		
Cured, *n* (%)	49 (73.1)	46 (56.8)	16.3	0.00 to 0.33
PP analysis				
TOC visit, *N*	66	81		
Cured or improved, *n* (%)	54 (81.8)	64 (79.0)	2.8	−0.11 to 0.17
Cured, *n* (%)	49 (74.2)	46 (56.8)	17.4	0.01 to 0.34

[a]Percentages refer to $n/N \times 100$.
[b]Clinical success (cure or improvement) rate in the cefoperazone-sulbactam arm minus that in the cefepime arm.

cefoperazone-sulbactam arm and that in the cefepime arm did not significantly differ (100% versus 75%; $P = 0.408$).

Microbiological responses. The ITT analysis showed no significant differences between microbiological eradication/presumed microbiological eradication rates in the study groups at both EPT visit (54.0% [27/50] versus 55.6% [25/45]; $P = 0.935$) and TOC visit (51.7% [15/29] versus 39.4% [13/33]; $P = 0.357$).

Safety evaluation. In safety analysis ($n = 166$), a total of 330 adverse events (AEs) were reported from 116 patients (69.9% [116/166]). Most of the AEs were graded as mild (66.1% [218/330]), and only 35 (10.6% [35/330]) of the reported AEs were judged to be causally related to the study antibiotics (Table 4). Among the 166 patients, the leading AE types were gastrointestinal (32.5%), respiratory (19.3%), metabolic (18.1%), and hematologic (12.7%) disorders. Among the overall AEs, 30 were of serious adverse events (SAEs).

Between the 2 treatment arms, there were no significant differences in the proportion of patients reporting AEs (73.4% versus 66.7%; $P = 0.398$) and SAEs (16.5% versus

TABLE 4 Summary of adverse events in the safety analysis

Adverse event[a]	Value(s) for treatment arm: Cefoperazone-sulbactam (*N* = 79)	Cefepime (*N* = 87)	*P* value
AE, N_1	160	170	
Patients with at least one AE, *n* (%)	58 (73.4)	58 (66.7)	0.398
SAEs, N_2	19	11	
Patients with SAEs, *n* (%)	13 (16.5)	7 (8.0)	0.151
Causality			
AEs related to drug, *n*	20	15	
Patients with AE related to drug, *n* (%)	14 (17.7)	13 (14.9)	0.677
Patients with SAE related to drug, *n* (%)	0 (0.0)	0 (0.0)	
Antibiotic discontinuation due to AE/SAE, *n* (%)	5 (6.3)	2 (2.3)	0.259
AE severity			
AE, N_1	160	170	
Mild, *n* (%)	96 (60.0)	122 (71.8)	
Moderate, *n* (%)	44 (27.5)	39 (22.9)	
Severe, *n* (%)	20 (12.5)	9 (5.3)	
Patients with AE, *n* (%)			
Mild	24 (30.4)	30 (34.5)	
Moderate	21 (26.6)	21 (24.1)	0.293
Severe	13 (16.5)	7 (8.0)	
SAE, N_2	19	11	0.056
Death, *n* (%)	7 (37.8)	2 (18.2)	0.281
Patients with AE, *n* (%)			
Mild	0/79 (0.0)	0/87 (0.0)	
Moderate	1/79 (1.3)	2/87 (2.3)	0.224
Severe	12/79 (15.2)	5/87 (5.7)	

[a]Percentages refers to $n/N \times 100$, unless stated otherwise.

TABLE 5 Clinical responses to treatments with cefoperazone-sulbactam and cefepime in the HAP and HCAP subgroups

Parameter	Clinical response			No. lost to follow-up	No. of clinical successes (rate, %)[a]	*P* value
	Cured, n_1	Improved, n_2	Failed, n_3			
ITT analysis						
Cefoperazone-sulbactam, $N = 71$						
HAP, $n = 7$ (10.0%)	2	1	4	0	3 (42.8)	0.004[b]
HCAP, $n = 64$ (90.0%)	47	5	8	4	52 (86.7)	0.673[c]
Cefepime, $N = 83$						
HAP, $n = 9$ (11.0%)	4	3	1	1	7 (87.5)	0.200[d]
HCAP, $n = 74$ (89.0%)	42	15	16	1	57 (78.1)	0.535[e]
PP analysis						
Cefoperazone-sulbactam, $N = 66$						
HAP, $n = 7$ (10.6%)	2	1	4	0	3 (42.9)	0.005[b]
HCAP, $n = 59$ (89.4%)	47	4	8	0	51 (86.4)	0.673[c]
Cefepime, $N = 81$						
HAP, $n = 8$ (9.90%)	4	3	1	0	7 (88.0)	0.216[d]
HCAP, $n = 73$ (90.1%)	42	15	16	0	57 (74.6)	0.535[e]

[a]Clinical success rates were determined as $(n_1 + n_2)/(n_1 + n_2 + n_3)$.
[b]Clinical success rates between HAP subgroup and HCAP subgroup treated with cefoperazone-sulbactam.
[c]Clinical success rates between HAP subgroup treated with cefoperazone-sulbactam and HAP subgroup treated with cefepime.
[d]Clinical success rates between HCAP subgroup treated with cefoperazone-sulbactam and HCAP subgroup treated with cefepime.
[e]Clinical success rates between HAP subgroup and HCAP subgroup treated with cefepime.

8.0%; $P = 0.151$), AEs judged to be causally related to the study antibiotics (17.7% versus 14.9%; $P = 0.677$), the severity of the AEs ($P = 0.293$), and patients experiencing different severities of AEs ($P = 0.224$) (Table 4). Of note, prolongations of prothrombin time and activated partial thromboplastin time were found in two patients on day 7 of the cefoperazone-sulbactam therapy and were corrected with vitamin K injection and transfusion of fresh frozen plasma. These patients were cured of their pneumonia after 11 days of cefoperazone-sulbactam treatment. SAEs are detailed in Table S1 in the supplemental material. No SAEs were judged to be causally related to the study drugs. Among the included patients, 7/79 (8.9%; 95% CI, 2.5% to 15.3%) and 2/87 (2.3%; 95% CI, 0% to 5.5%) fatalities were found in the cefoperazone-sulbactam and the cefepime groups, respectively ($P = 0.087$), and none of them were judged to be causally related to the antibiotics.

HAP versus HCAP subgroups. The majority of the included patients suffered HCAP. Similar demographics and underlying diseases were found in patients in the HAP and HCAP subgroups (Table S2). At TOC, both the ITT and PP analyses (Table 5) showed that there was no significantly different clinical success rate between the HAP subgroups treated with cefoperazone-sulbactam and cefepime and between the HCAP subgroups treated with cefoperazone-sulbactam and cefepime. However, in the cefoperazone-sulbactam arm, a significantly higher success rate was found in the HCAP subgroup than in the HAP subgroup.

DISCUSSION

Although the vast majority of cases in this study were HCAP, similar advanced ages and multiple comorbidities found in the HAP and HCAP subgroups suggested a similar vulnerability of patients in both subgroups. The major findings of this comparative trial can be summarized as the following: (i) cefoperazone-sulbactam was noninferior to cefepime in the treatment of HAP/HCAP, and (ii) there were no significant differences in microbiological eradiation rate, chest radiographic consolidation/infiltration resolution rate, AEs, and SAEs between the cefoperazone-sulbactam and cefepime groups. Although additional analysis disclosed a higher clinical success rate (86.4% versus 42.9%; $P = 0.005$) between the HCAP ($n = 64$) and HAP ($n = 7$) subgroups in the cefoperazone-sulbactam arm, further study with a much larger sample size of HAP is needed to verify this finding.

Although cefoperazone is, in general, efficacious against *Enterobacteriaceae* members, *P. aeruginosa*, and other non-glucose-fermenting GNB *in vitro* (13, 14), it has not

been widely used, probably because cefoperazone is slightly less stable to some β-lactamases (13), its MICs are influenced by high-inoculum concentrations of β-lactamase-producing bacterial strains (13, 19), and its *N*-methylthiotetrazole (NMTT) side chain potentially induces transient hypoprothrombinemia, putting patients at risk of bleeding (20). Previous reports indicated that by combination with sulbactam, the stability of cefoperazone to β-lactamases was markedly augmented (13, 15–18), and the bacterial inoculum effect against cefoperazone was overcome (17, 19). As NMTT-containing cephalosporins and cephamycins are relatively weak inhibitors of vitamin K epoxide reductase, hypoprothrombinemia induced by cefoperazone was rare in the general patient population but was occasionally found in patients with malnutrition (20, 21), patients concurrently receiving anticoagulants, and those who experienced hemorrhagic events within the prior 6 months (21); hypoprothrombinemia is reversible with 1 mg of vitamin K given intravenously (20).

An advantage of using cefoperazone-sulbactam over cefepime is the additional coverage of anaerobes (13, 22), which are occasionally encountered copathogens in HAP/HCAP (23, 24). High rates of MDR pathogens were found in patients with clinically severe HCAP in some geographic locales, like Taiwan (6, 7, 9). Of note, sulbactam *per se* has been widely reported to be effective against *Acinetobacter* species (25, 26), which are often found to be pathogens in HAP (1, 23, 27, 28). There was no selection of resistance found in serial microbiological evaluations in either arm.

There are a few limitations to this study. First, it lacked the measurement of clinical severities at the patients' entry to the study. Second, a limited number of HAP/HCAP cases involved clearly identified pathogens, and a limited number of cases were available for evaluation of microbiological eradication rate. Third, the dosing for cefepime used in this study seems suboptimal today in terms of pharmacokinetics/pharmacodynamics (29). Fourth, the study was subjected to the inherent limitations of an open-label study. However, this study also has several strengths. As it was conducted at multiple large centers, the severities of the pneumonia cases of patients admitted to these facilities were theoretically higher than those treated at regional hospitals. Moreover, potential biases in interpretations of the antibiotic therapeutic outcomes were minimized by adopting the conclusions of an independent blinded evaluator in case disagreements were found between the principal investigator and blinded evaluator.

In summary, our data suggest that cefoperazone-sulbactam is noninferior to cefepime in treating HAP/HCAP; further study is needed to consolidate our findings.

MATERIALS AND METHODS

Study design, hospital settings, and patients. This is a randomized, multicenter, open-label, noninferiority trial evaluating the efficacy and safety of cefoperazone-sulbactam versus cefepime in the treatment of patients suffering HAP/HCAP. The study was conducted between 22 September 2009 and 6 August 2012 at multiple centers in Taiwan. Participating medical centers and their capacities are the following: Taipei Veterans General Hospital (3,046 beds), Kaohsiung Chang Gung Memorial Hospital (2,686 beds), Kaohsiung Medical University Hospital (1,702 beds), Wan Fang Medical Center (726 beds), Tri-Service General Hospital, National Defense Medical Center (1,903 beds), Chang Gung Memorial Hospital at Linkou (3,406 beds), E-Da Hospital (1,251 beds), Chi-Mei Medical Center (1,278 beds), Shuang-Ho Hospital (1,130 beds), National Cheng Kung University Hospital (1,000 beds), Chung Shan Hospital (1,305 beds), and Kaohsiung Veterans General Hospital (1,455 beds). This study was approved by the Joint Institutional Review Board in Taiwan and by the Institutional Review Board of each participating hospital.

Definitions and inclusion and exclusion criteria. HAP referred to pneumonia developed ≥48 h after hospitalization, and ventilator-associated pneumonia referred to HAP that developed in a patient receiving mechanical ventilation for ≥48 h. HCAP referred to pneumonia in patients with extensive health care contact (i.e., hospitalization in the previous 90 days, residence in a nursing home, and/or receipt of chronic dialysis) (23).

Eligible subjects for recruitment were male or female aged ≥18 years suffering a pneumonia that fit the criteria of either HAP or HCAP. The diagnosis of pneumonia was made based on the newly developed or progressive radiographic lung infiltration/consolidation in patients with 2 or more of the following: cough, fever (>38.5°C), hypothermia (<35°C), purulent sputum or respiratory secretion, peripheral white blood cell (WBC) count of >10,000/μl or >15% cell band of the peripheral WBCs, characteristic clinical presentation(s) (i.e., auscultatory rales and/or bronchial breath sounds), and hypoxemia (i.e., arterial partial oxygen pressure [PaO_2] of <60 mm Hg when breathing room air or ≥25% decrease in the PaO_2 compared with the initial value).

Eligible subjects for recruitment were pneumonia patients who did not receive parenteral antibiotic therapy for ≥24 h before inclusion or patients whose pneumonia was deteriorating despite receiving antibiotic therapy, and the results of their bacterial culture and susceptibility testing suggested that the study antibiotics were therapeutically indicated. The study was registered with the Center for Drug Evaluation (CDE), Taiwan (TTYCS0501; http://www1.cde.org.tw/ct_taiwan/search_case2_tornado.php?caseno=245). Written consent was obtained from all recruited subjects.

Once an eligible subject was recruited, blood and sputum were sampled for culture and susceptibility testing for the isolated pathogen(s). Bacterial culture, identification, and susceptibility testing using the disk diffusion method were carried out on a clinical practice basis. Bacterial identifications were performed using conventional methods and/or an automated identification system as described elsewhere (27); the cutoff diameter of the inhibitory zone for judging GNB susceptibility to cefoperazone-sulbactam was based on that for judging susceptibility to cefoperazone alone (30). Sputum specimens were additionally subjected to Gram staining; a sputum specimen that revealed >25 polymorphonuclear neutrophils and <10 squamous epithelial cells per low-power field (LPF) (×100) was regarded as a good-quality one.

Exclusion criteria were the following: known active infection with pathogen(s) resistant to cefoperazone-sulbactam or cefepime; pregnancy or breastfeeding; known bronchial obstruction or a history of postobstructive pneumonia; peripheral neutrophil count of <1,000/μl; known active pulmonary infection caused by virus, fungus, *Legionella* species, or *Mycobacterium* species; known underlying human immunodeficiency virus infection; a good-quality sputum specimen disclosing predominant clusters of Gram-positive cocci; receipt of any investigational drug within 30 days before recruitment; prerecruitment serum level of aspartate aminotransferase, alanine aminotransferase, creatinine, or blood urea nitrogen ≥3 times the upper limit of its normal range; previous hypersensitivity to penicillins, cephalosporins, carbapenems, or β-lactam/β-lactamase inhibitors; short expected survival time due to profound sepsis; and the presence of severe complications (e.g., septic shock, acute respiratory distress syndrome, and multiple-organ failure).

Randomization and masking. Patients who met the inclusion criteria were invited to participate in the study. Participants were randomly assigned by sealed, opaque, and numbered envelopes to different treatment arms to receive either intravenous cefoperazone-sulbactam (2 g of each) (TTY Biopharm Company, Taiwan) or cefepime (2 g) (Bristol-Myers Squibb, Taiwan) per 12 h. This cefepime dosing was recommended by the pharmaceutical company for treatment of pneumonia and was widely used around the study period (31, 32).

Procedures. The antibiotic therapeutic intervals ranged from 7 to 21 days in each arm. The treatment duration, discontinuation, and/or modification was at the discretion of the treating physician/investigator; they were allowed to prescribe additional antimicrobials targeting Gram-positive cocci or antifungal agents if superimposing infections occurred during the trial. Clinical signs and symptoms, microbiological results, chest-radiographic evolutions, and clinical and laboratory safety were assessed and recorded throughout the treatment course.

Outcomes. Outcome evaluations were done based on all available information at the early post-therapy (EPT) visit and test-of-cure (TOC) visit within 3 days and 7 to 21 days after completing the antibiotic treatment, respectively.

The primary efficacy endpoint was clinical responses of HAP/HCAP to the antibiotic treatment, which involved clinical success and failure. Clinical success was defined as cure/improvement, i.e., complete/partial resolution of pneumonia signs and symptoms with improvement or lack of progression of lung infiltration/consolidation found at the follow-up chest radiography. In contrast, clinical failure was defined as (i) clinically stationary or progressive HAP/HCAP after 3 to 5 days of antibiotic therapy, (ii) emergence of a new pulmonary infection that mandated changing or adding antimicrobial(s) to the study drugs, (iii) progression of lung infiltration/consolidation found at the follow-up chest radiography, (iv) initial clinical improvement followed by marked clinical deterioration after 3 to 5 days of antibiotic therapy, and/or (v) death resulting from clinically unrelenting pneumonia.

In order to minimize the possible bias in result interpretations, clinical and evolutionary chest-radiographic outcomes evaluated by the investigators were subjected to additional outcome assessments by another blinded infectious disease specialist who had no knowledge of the antibiotic being administered to each patient. In cases where the interpretation of the blinded evaluator was not in agreement with that of the investigators, the former was regarded as the unbiased outcome and was included in this report.

The secondary efficacy endpoint was microbiological responses based on culture results of sputum sampled on days 4, 7, 14, and 21 after starting the antibiotic therapy and at the EPT visit, which involved eradication, persistence, superinfection, and colonization. Eradication was defined as elimination of the possible causative organism(s), which was indicated by culture results of a sputum specimen with <10 squamous epithelial cells/LPF. Cases with sputum no longer available for evaluation as a result of clinical improvement were referred to as presumed eradication. Persistence was defined as failure to eradicate the original possible causative organism. Superinfection was defined as the growth of a new microbe(s) from a good-quality sputum specimen sampled from a patient with signs and symptoms and/or chest radiographic findings consistent with ongoing pneumonia.

All included patients were monitored for adverse events (AEs), serious adverse events (SAEs), and adverse drug reactions (ADRs) throughout their treatment courses and at the EPT and TOC visits. An ADR was defined as harm causally related to the study medication. Any toxicity that emerged during the study and was not clearly attributable to other causes after the antibiotic discontinuation was considered

causally related to the study antibiotic. All AEs were coded using the AE coding system of the *Medical Dictionary for Regulatory Activities* (https://www.meddra.org/).

In addition, to clarify whether treatment effects of these antibiotics for HAP and HCAP differed, the included patients were further separated into those with HAP and those with HCAP subgroups for further analyses of their responses to different antibiotic treatments.

Statistical analysis. The 95% confidence interval (CI) for the difference in success rate (percentage of treatment success in the cefoperazone-sulbactam arm minus that in the cefepime arm) was calculated based on the normal approximation to the binomial distribution. The noninferiority test was based on the lower boundary of the 95% CI for the difference in success rate lying within the noninferiority margin of 20% and the upper boundary of 0% (33–35). Based on previous reports (36), assuming a treatment success rate of approximately 75% in each arm, a statistical power of 80%, a one-sided significance level of 0.025, and an evaluability rate of 70%, the study would enroll 204 subjects to obtain 142 available for evaluation. This sample size would yield acceptable differences in success rate at reasonable study costs.

Intent-to-treat (ITT), per-protocol (PP), and safety analyses were performed. All patients who received at least one dose of either cefoperazone-sulbactam or cefepime were subjected to safety analysis. With the exception of 12 patients who were lost to follow-up and 2 who were found at a regular audit to be recruited and received antibiotic trial at a branch hospital of one of the study centers, all patients who were randomized and received at least one dose of a study drug were grouped as the ITT population. Inclusions of the 2 patients and conducting of the antibiotic trial at the branch hospital rather than at the center where it was registered as a study site were regarded as a violation of the study protocol. The PP population included patients who had received a study drug for at least 7 days and were fully evaluable at the last follow-up assessment.

Comparisons of demographic, clinical, laboratory, and chest-radiographic data between different arms/groups/subgroups were performed. For hypothesis testing, the Student's *t* test was used for normally distributed variables and the Mann-Whitney *U* test for skewed distributions. Fisher's exact test, χ^2 test, or Cochran-Mantel-Haenszel test was used for categorical variables as necessary. Wilcoxon signed-rank test was specifically used to evaluate the antibiotic treatment responses at the EPT and TOC assessments by separately comparing the posttreatment conditions at different time points with the pretreatment conditions. Results were considered statistically significant at a *P* value of <0.05. Statistical analyses were performed using the SAS software package, version 9.0 (SAS Institute Inc., NC).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.00023-19.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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