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Efficacy of cefepime versus ceftazidime in the treatment of adult pneumonia

Jung-Chung Lin, Kuo-Ming Yeh, Ming-Yieh Peng, Feng-Yee Chang

Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC

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Effective empiric treatment of pneumonia requires antibiotic coverage against gram-negative and gram-positive pathogens, including drug-resistant isolates. This study evaluated the efficacy of cefepime treatment in 20 patients with community-acquired pneumonia (CAP) and 21 patients with hospital-acquired pneumonia (HAP), and ceftazidime treatment in 20 patients with HAP. The mean age of patients was over 70 years. More than half of the patients had multiple lobe involvement. There was no significant difference in the severity of illness according to the acute physiology, age, chronic health evaluation (APACHE) III score between the HAP-cefepime and HAP-ceftazidime group. The most common bacteria isolated from sputum of patients with CAP were *Streptococcus pneumoniae* (n = 7), *Klebsiella pneumoniae* (n = 4), and *Pseudomonas aeruginosa* (n = 2). In patients with HAP, *P. aeruginosa* (n = 13), *Acinetobacter baumannii* (n = 11), *Serratia marcescens* (n = 6), *K. pneumoniae* (n = 5), *Stenotrophomonas maltophilia* (n = 5), *Enterobacter cloacae* (n = 3), *Citrobacter* spp. (n = 2), and *Escherichia coli* (n = 2) were isolated. The cure rates were 95%, 76%, and 60% in the CAP-cefepime group, the HAP-cefepime group, and the HAP-ceftazidime group, respectively. The increased rates of antimicrobial resistance commonly found among isolates causing CAP and HAP indicate that extended-spectrum antimicrobial agents, such as cefepime, would be more appropriate therapeutic agents.

Key words: Cefepime, ceftazidime, community-acquired pneumonia (CAP), efficacy, hospital-acquired pneumonia (HAP)

Pneumonia continues to be an important cause of morbidity and mortality despite recent progress in its treatment [1]. Many different organisms colonize the nasopharynx and tracheobronchial epithelium, and this makes it often difficult to determine a precise causative pathogen, even in patients whose sputum culture is obtained [2]. The treatment of pneumonia is therefore generally empiric and is based on the knowledge of the most prevalent pathogens, the clinical setting, and drug-resistance patterns in a geographic area. Empiric treatment must consider the possible roles of gram-positive organisms, particularly *Streptococcus pneumoniae* and *Staphylococcus aureus*, as well as gram-negative organisms, particularly *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Enterobacter* species, and *Klebsiella pneumoniae* [2].

Cefepime, a new injectable "fourth-generation" cephalosporin, has an extended spectrum of activity against both gram-positive and gram-negative organisms [3]. Its activity against methicillin-sensitive *S. aureus*, *S. pneumoniae*, the majority of *Enterobacter* spp., *P. aeruginosa*, and other members of the *Enterobacteriaceae* makes it particularly attractive for the management of severe pneumonia [3]. Cefepime showed promising results in initial trials in treating severe community-acquired and nosocomial infections [4,5]. In this study, the efficacy of empiric use of cefepime versus ceftazidime as initial parenteral therapy for hospitalized pneumonia patients was evaluated.

Materials and Methods

Study design and patients enrollment

This comparative study assessed the efficacy of cefepime versus ceftazidime in the treatment of hospital-acquired pneumonia (HAP). The efficacy of cefepime for the treatment of hospitalized patients with community-acquired pneumonia (CAP) was also assessed. The inclusion criteria were as follows: age of 18 years or older, human immunodeficiency virus (HIV)-negative, evidence of a new pulmonary infiltration on chest radiograph consistent with aus-

Corresponding author: Dr. Feng-Yee Chang, Division of Infectious Diseases and Tropical Medicine, Tri-Service General Hospital, 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan, ROC.

cultatory findings, purulent sputum and at least two of the following findings: fever (≥ 38°C) or hypothermia (≤ 36°C), tachypnea (≥ 20 /min), tachycardia (≥ 90 /min), and leukocytosis (≥ 12 000 /mm^3 or ≥ 10% immature or "band" neutrophils) [6]. Exclusion criteria were previous treatment with cefepime or ceftazidime for the existing episode of pneumonia, a history of hypersensitivity to a cephalosporin or penicillin antibiotic, pregnancy or breast-feeding, leukocyte count of less than 2000 /mm^3, severe disease which may limit survival during therapy and follow-up period, and likely requirement of long term (≥ 14 days) antimicrobial treatment of the underlying infection (eg empyema, endocarditis, osteomyelitis). Diagnostic studies included blood culture, gram staining and culture of expectorated sputum [7]. Patients who met the criteria for enrollment were randomized into each arm of the study by random sampling.

Study procedures

On entering the study, each patient's medical history was recorded and physical examination, chest radiography, sputum and blood culture, and antibiotic susceptibility testing were performed. Clinical laboratory studies included hematology, serum chemistry analysis, and urinalysis. During therapy, clinical evaluations of the efficacy and safety of the treatment were performed daily during the first week of treatment and every 2 to 3 days thereafter. Clinical laboratory studies were repeated twice weekly during the first week, weekly thereafter during therapy, and within 72 h at the discontinuation of therapy. A post-treatment evaluation, performed within 72 h at the completion of therapy, included a clinical evaluation to determine the presence or absence of signs and symptoms of pneumonia or adverse events, a culture analysis of a sputum or lower respiratory tract sample, and a chest radiography.

Drug administration

Patients with CAP received cefepime (1-2 gm/12 h) treatment after completing the gram stain study and clinical evaluation. Patients with HAP received cefepime 1 to 2 gm every 12 h intravenously or ceftazidime 1 to 2 gm every 8 h intravenously according to their group assignments. The dosage of cefepime and ceftazidime was adjusted according to renal function. The recommended length of therapy was 10 to 14 days, or at least 24 to 48 h after resolution of signs and symptoms of infection. Patients were scheduled to receive treatment for a minimum of 5 days. When *P. aeruginosa* or methicillin-resistant *S. aureus* (MRSA) infection was considered, a combined therapy with aminoglycosides or glycopeptides, respectively, should be indicated [7,8]. If an atypical pathogen could not be excluded at the start of treatment in this study, a macrolide combination was used.

Definitions

Hospital-acquired pneumonia was defined as the development of pneumonia at least 48 h after hospitalization or as the development of pneumonia related directly to a hospital intervention and not incubating at the time of admission [8], whereas CAP was defined as pneumonia acquired in the community not related to a hospital intervention, and in a patient who had not been recently hospitalized in any acute-care facility and was not a nursing home resident.

Microbiology and susceptibility testing

At least two sets of blood culture were performed for each patient before starting the study treatment. The blood culture isolates were considered pathogens except for common skin contaminants such as *Bacillus* spp., coagulase-negative *Staphylococcus* or *Corynebacterium* spp., or when isolates were from purulent sputum (presence of ≥ 25 leukocytes and ≤ 10 epithelial cells per low power field) obtained by sterile suctioning or deep-cough expectoration in patients with bacterial pneumonia.

Serologic tests for atypical pathogens including IgM for *Mycoplasma pneumoniae* (International immunodiagnostic), specific IgM, IgG, and IgA for *Chlamydia pneumoniae* (Savyon, Diagnostics LTD, Israel), indirect fluorescent antibody of acute and convalescent sera for *Legionella pneumophila* (Zeus, Raritan, NJ, USA), and urinary antigen for *L. pneumophila* serogroup 1 (Binax, Portland, USA) were performed in the CAP group. None of the patients with CAP was infected by atypical pathogens.

All pathogens were tested for *in vitro* susceptibility to cefepime and ceftazidime by the disk diffusion methods described by the National Committee for Clinical Laboratory Standards [9].

Evaluation of efficacy

Patients with clinical and laboratory findings consistent with bacterial pneumonia were evaluated for clinical and bacteriologic response to treatment. Clinical response was the primary endpoint, whereas bacteriologic response was the secondary endpoint. Clinical response was determined basing on the findings of physical examination and status of infection-related signs and symptoms. The blood cell count, bio-

Table 1. Demographic data, comorbid illness, and severity in patients with community-acquired pneumonia treated with cefepime, and hospital-acquired pneumonia treated with cefepime versus ceftazidime

Category	Cefepime CAP (n = 20)	Cefepime HAP (n = 21)	Ceftazidime HAP (n = 20)
Age (mean ± S.D.)	71.3 ± 11.7	74 ± 18.8	72.3 ± 2.4
Male:Female (%)	60:40	48:52	70:30
Comorbid disease			
Vascular disorder			
HCVD	9	7	2
CAD	2	3	3
VHD	1	2	1
CVA	4	3	4
COPD	1	5	3
Diabetes mellitus	1	3	3
Renal insufficiency	3	3	1
Parkinsonism	3	0	0
Senile dementia	2	1	0
SLE	1	0	0
Symptom/sign			
Fever	17	18	19
Cough	9	3	1
Shortness of breath	3	4	6
APACHE III (mean ± SD)	34 ± 15	50 ± 23	44 ± 19
Bacteremia	1	2	1
Radiographic findings			
Single lobe	8	9	5
Multiple lobes	12	12	15

Abbreviations: CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCVD = hypertensive cardiovascular disease; CAD = coronary artery disease; VHD = valvular heart disease; CVA = cerebral vascular accident; COPD = chronic obstructive pulmonary disease; SLE = systemic lupus erythematosus; APACHE = acute physiology, age, chronic health evaluation

chemistry, and chest radiograph were followed every week during the treatment. Bacteriologic response was measured by the results of cultures obtained before, during, and after the completion of treatment.

Cure was defined as complete resolution of clinical signs and symptoms related to the existing episode of pneumonia, or improvement without complete resolution but lack of progression on radiographic findings. Failure was defined as persistence or worsening of the clinical signs or symptoms of the existing episode of pneumonia, or the appearance of new clinical signs and symptoms relevant to this episode of pneumonia at the end of therapy. The bacteriologic response of the original infection was classified as follows: eradication was defined as the absence of pathogen isolated pre-therapy in cultures taken during or post-therapy; persistence was defined as isolation of the pathogen isolated pre-therapy in the final post-therapy culture.

Statistical analysis

The significance of differences in characteristics between patients with HAP who received cefepime and ceftazidime therapy was analyzed using analysis of variance and chi-square test. A p value less than 0.05 was considered to be significant.

Results

Patient characteristics

Of the 61 patients, 20 patients with CAP received cefepime treatment, and 41 with HAP were randomized to either the cefepime group (n = 21) or the ceftazidime group (n = 20). Women accounted for 41% (25/61) of all pneumonia patients in this study. The mean age of patients in each group was over 70 years (Table 1). Most patients in each group had comorbid illness including hypertensive cardiovascular disease, cerebrovascular accident, coronary artery disease, chronic obstructive pulmonary disease, diabetes mellitus, or renal insufficiency (Table 1). More than half of the patients with pneumonia had multiple lobe involvement (Table 1). Cough was noted more often in patients with CAP than in patients with HAP (45% vs 10%, $p < 0.05$). Severity of illness grading by acute physiology, age, chronic health evaluation (APACHE) III score was

Table 2. Outcome of patients with community-acquired pneumonia treated with cefepime, and hospital-acquired pneumonia treated with cefepime versus ceftazidime

Variable	Cefepime CAP, n = 20 (%)	Cefepime HAP, n = 21 (%)	Ceftazidime HAP, n = 20 (%)
Days of antibiotic treatment (mean ± SD)	8.8 ± 2.6	10.2 ± 3.5	10.2 ± 4.0
Combination antibiotic			
Aminoglycoside	1	6	15
Clarithromycin	6	1	0
Glycopeptides	0	3	3
Clinical outcome			
Cure	19 (95)	16 (76)	12 (60)
Failure	1 (5)	5 (24)	8 (40)

Abbreviations: CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia

Table 3. Bacteriologic data in patients with community-acquired pneumonia treated with cefepime and hospital-acquired pneumonia treated with cefepime versus ceftazidime

Microorganism	Cefepime CAP, n = 20 (%)	Cefepime HAP, n = 21 (%)	Ceftazidime HAP, n = 20 (%)
S. pneumoniae	7 (35)	0	0
Viridans streptococci	1 (5)	0	0
MRSA	1 (5)	5 (24)	5 (25)
P. aeruginosa	2 (10)	3 (14)	10 (50)
A. baumannii	0	6 (29)	5 (25)
K. pneumoniae	4 (20)	2 (10)	3 (15)
S. marcescens	1 (5)	3 (14)	3 (15)
S. maltophilia	0	1 (5)	4 (20)
E. cloacae	0	2 (10)	1 (5)
Citrobacter spp.	0	2 (10)	0
E. coli	0	0	2 (10)
M. morganii	0	0	1 (5)
Achromobacter sp.	0	0	1 (5)
Polymicrobial	3 (15)	10 (48)	11 (55)
Monomicrobial	8 (40)	4 (19)	6 (30)
Unknown etiology	7 (35)	7 (33)	3 (15)

Abbreviations: CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; MRSA = methicillin-resistant *S. aureus*

similar in the HAP-cefepime and the HAP-ceftazidime group (50 ± 23 [SD] vs 44 ± 19, $p = 0.36$) (Table 1). None of the patients showed serologic evidence of atypical pneumonia.

Clinical response

The mean duration of antibiotic treatment was 8.8 ± 2.6 days for the CAP-cefepime group, 10.2 ± 3.5 days for the HAP-cefepime group, and 10.2 ± 4 days for the HAP-ceftazidime group. The cure rate at the end of therapy was 95% for the CAP-cefepime group, 76% for the HAP-cefepime group, and 60% for the HAP-ceftazidime group (Table 2). Patients in the HAP-ceftazidime group received an aminoglycoside combination more often than patients in the HAP-cefepime group (75% vs 29%, $p = 0.0029$).

In the CAP-cefepime group, one patient failed to respond and developed acute respiratory distress syndrome during treatment. In the HAP-cefepime group, five patients failed to respond to treatment, including one patient who developed new pulmonary infiltration during treatment, two patients whose symptoms and signs worsened, one who developed acute respiratory distress syndrome and died, and one who developed hyperkalemia and died. Eight patients in the HAP-ceftazidime group failed to respond to treatment, including one patient who developed acute renal failure, one with new pulmonary infiltration, and six with worsening of symptoms and signs.

Bacteriology and bacteriological response

Methicillin-susceptible *S. aureus* and viridans streptococci bacteremias were isolated from one patient in the CAP-cefepime group. There were two patients with

Table 4. Susceptibility of isolated organisms in patients with hospital-acquired pneumonia treated with cefepime versus ceftazidime

Microorganism	Cefepime (n = 21)		Ceftazidime (n = 20)	
	S	R	S	R
P. aeruginosa	2	1	10	0
A. baumannii	4	2	2	3
K. pneumoniae	2	0	2	1
S. marcescens	3	0	2	1
S. maltophilia	0	1	1	3
E. cloacae	2	0	0	1
Citrobacter spp.	2	0	0	0
E. coli	0	0	2	0
M. morganii	0	0	1	0
Achromobacter sp.	0	0	1	0
Concomitant MRSA	0	5	0	5

Abbreviations: HAP = hospital-acquired pneumonia; S = susceptible; R = resistant; MRSA = methicillin-resistant *S. aureus*

P. aeruginosa and *Serratia marcescens* bacteremia, respectively, in the HAP-cefepime group. There was one patient with *P. aeruginosa* bacteremia in the HAP-ceftazidime group (Table 1). All of these patients with bacteremia responded well to treatment with cefepime or ceftazidime.

A total of 75 organisms were isolated from the sputum of the 61 patients (16 in the CAP-cefepime group, 24 in the HAP-cefepime group, and 35 in the HAP-ceftazidime group) (Table 3). The most common pathogens in patients with CAP were *S. pneumoniae* (n = 7), *K. pneumoniae* (n = 4), and *P. aeruginosa* (n = 2). The pathogens isolated in patients of the HAP-cefepime group were *Acinetobacter baumannii* (n = 6), *P. aeruginosa* (n = 3), *S. marcescens* (n = 3), *Enterobacter cloacae* (n = 2), *Citrobacter* spp. (n = 2), and *K. pneumoniae* (n = 2). In the HAP-ceftazidime group, the isolated pathogens were *P. aeruginosa* (n = 10), *A. baumannii* (n = 5), *Stenotrophomonas maltophilia* (n = 4), *K. pneumoniae* (n = 3), *S. marcescens* (n = 3), and *E. coli* (n = 2). Monomicrobial infection was more common in the CAP group (40% vs 15%, $p = 0.076$). In contrast, polymicrobial infection was more common in the HAP group (51% vs 25%, $p < 0.05$).

One patient in the CAP group who failed to respond to cefepime treatment had no organism identified and no serologic evidence of atypical pathogen infection. The five treatment failures in the HAP-cefepime group had gram-negative sputum isolates of cefepime-resistant strains including *P. aeruginosa* (n = 1), *A. baumannii* (n = 2), and *S. maltophilia* (n = 1). Persistent *E. cloacae* infection was isolated from the sputum of two patients although the *in vitro* antibiogram was susceptible to cefepime. The eight treatment failures in the HAP-ceftazidime group were related to the presence of eight ceftazidime-resistant isolates in their sputum, namely, *S. maltophilia* (n = 3), *A. baumannii* (n = 3), *S. marcescens* (n = 1), and *K. pneumoniae* (n = 1). There were two strains of *P. aeruginosa*, one strain of *E. coli*, and one strain o *Morganella morganii*, which were susceptible to ceftazidime *in vitro* (Table 4).

Adverse events

One patient in the HAP-cefepime group developed skin rash and one patient in the HAP-ceftazidime group developed diarrhea.

Discussion

In this study, *S. pneumoniae*, *K. pneumoniae*, and *P. aeruginosa* were the most common organisms found in patients with CAP, while *P. aeruginosa*, *A. baumannii*, *S. marcescens*, *K. pneumoniae*, and other *Enterobacteriaceae* were the most common organisms identified in patients with HAP. The broad spectrum activity of cefepime against *S. pneumoniae*, *H. influenzae*, *Enterobacteriaceae*, *Pseudomonas* spp., and methicillin-susceptible *S. aureus* makes it a candidate for the treatment of respiratory infections in debilitated patients [10].

The majority of patients in the treatment groups achieved a satisfactory clinical response: 95% of cefepime-treated patients with CAP, 76% of cefepime-treated patients with HAP, and 60% of ceftazidime-treated patients with HAP. In the CAP group, six patients received clarithromycin combination until their urinary antigen test for *L. pneumophila* and serologic tests for atypical pathogens showed negative results. The pathogens most commonly isolated in HAP have been demonstrated to be multi-drug resistant enteric gram-negative bacilli and *S. aureus*. Therefore, combined therapy of aminoglycosides with glycopeptides was used in this study. Our results show that cefepime was highly effective, and at least equivalent to ceftazidime in efficacy for the treatment of nosocomial pneumonia. The success rates in this study were similar to previous studies of patients with pneumonia treated with cefepime versus ceftazidime [11,12].

The cases in which treatment failed in the HAP-cefepime and the HAP-ceftazidime group were similar in the presence of resistant strains. The most common resistant strains in the HAP-cefepime group included *A. baumannii*, *S. maltophilia*, *P. aeruginosa* and concomitant MRSA. The most common resistant strains in the HAP-ceftazidime group included *A. baumannii*, *S. maltophilia*, *P. aeruginosa*, *S. marcescens* and *K.*

pneumoniae. Increasing resistance of strains would be an important and serious problem in clinical practice.

In this study, adverse events occurred in one of the 41 cefepime-treated patients who developed skin rash, and in one of the 20 ceftazidime-treated patients who developed diarrhea. In a previous study, the most common adverse events associated with cefepime treatment were headache (2.4%), nausea (1.8%), rash (1.8%), and diarrhea (1.7%) [13]. The most commonly observed adverse events associated with ceftazidime treatment were diarrhea (3.2%), headache (2.5%), nausea (2.1%), rash (1.9%), and constipation (1.5%) [13].

Gram-negative bacilli are increasingly capable of producing AmpC β-lactamase and therapy harbor resistance to most antimicrobial agents. Jones *et al* [14] confirmed that both carbapenems and cefepime possess *in vitro* potencies against current clinical strains of gram-negative bacilli including *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and indole-positive *Proteus*. In Taiwan, Wang *et al* [15] demonstrated that the activity of cefepime against most gram-negative bacilli including *E. coli*, *K. pneumoniae*, *Acinetobacter* spp., *P. aeruginosa*, *Enterobacter cloacae* and *S. marcescens* was better than that of ceftazidime, except for *Burkholderia cepacia* and *S. maltophilia*. Among gram-positive cocci, cefepime was found to be active against most isolates of methicillin-susceptible staphylococci, *S. pyogenes*, viridans streptococci and *S. pneumoniae* [15].

In this study, polymicrobial infection was significantly more common than monomicrobial infection in HAP (51% vs 25%, $p < 0.05$), and monomicrobial infection was more common than polymicrobial infection (40% vs 15%, $p = 0.076$) in CAP. It is often difficult to determine a precise causative pathogen, even in patients whose sputum cultures were obtained. Many different organisms colonize the nasopharynx and tracheobronchial epithelium. Fagon *et al* [16] demonstrated that the use of fiberoptic bronchoscope to directly sample a suspected area and the use of quantitative culture to distinguish infecting pathogens from colonization microorganisms significantly decreased the number of polymicrobial organisms considered as pathogens in nosocomial pneumonia. Moreover, this technique improves survival rate, decreases antibiotic use and is associated with few organs failure in nosocomial pneumonia [16].

In this randomized study, cefepime was highly effective in the treatment of CAP and nosocomial pneumonia. Because of its extreme stability to hydrolysis by β-lactamase and low binding affinity to β-lactamase, cefepime is active against many isolates that are resistant to other β-lactams, including ceftazidime [17,18]. In conclusion, the results of this study indicate that cefepime is a good choice for the treatment of CAP and HAP caused by gram-positive cocci and gram-negative aerobes including *P. aeruginosa*.

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