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Efficacy and safety of cefepime in the treatment of serious bacterial infections in hospitalized adult patients

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Proper and timely choice of the antibiotic therapy for the management of infection in hospitalized patients is an immense challenge to the clinician. A newly developed extended-spectrum fourth-generation cephalosporin — cefepime, has been shown to have good activity against both gram-positive and gram-negative organisms. In order to further establish the efficacy and safety of cefepime in the treatment of adult hospitalized patients in Taiwan, we reviewed the medical records of all patients who received cefepime therapy for more than 72 h at the National Taiwan University Hospital during the period from January 1999 to April 1999. A total of 55 patients were treated with cefepime during this period. Thirty-two of them were males and 23 were females. Their ages ranged from 16 to 94 years old (average, 67). All had severe infections with a mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 18. More than half (56%) of the infections were nosocomial. The most common infections included pulmonary infection (49%), intra-abdominal infection (27%), skin and soft tissue infection (15%), febrile neutropenia (7%), and intravascular device infection (5%). All but one of the patients (98%) had pre-existing medical disease. Malignancy (49%) was the most common underlying illness. *Pseudomonas aeruginosa* (23 isolates) and *Enterobacter cloacae* (21) were the most common pathogens causing infections. Thirty-one (58%) of the patients were effectively treated with cefepime. Twenty of the patients died during the study period with most deaths attributable to persistent microbial infection and superinfection, especially *Acinetobacter baumannii* and fungal infection. Adverse effects developed in six patients, including eosinophilia (3 patients), leukopenia (2), skin rash (1), and drug related fever (1), but all were mild and transient. The results of this study show that cefepime is a safe and effective agent in the treatment of adult patients with severe infection in Taiwan.

Key words: Cefepime, hospitalized patients, sepsis, serious infection

Severe bacterial infection is one of the leading causes of death in hospitalized patients. Appropriate antimicrobial therapy reduces morbidity and mortality in patients with severe bacterial infection. Extended-spectrum cephalosporins have been established as safe and effective agents when given as empirical monotherapy to both non-neutropenic and neutropenic patients with severe bacterial infections [1,2]. A member of the new generation of expanded-spectrum cephalosporins, cefepime, has been evaluated for the treatment of a variety of severe bacterial infections and showed favorable responses [3-5]. The results suggest that cefepime is effective in empirical therapy in neutropenic fever patients and as a monotherapy for immunocompromised patients [6,7]. Against genera which characteristically produce Bush group 1 cephalosporinases [8], the intrinsic potency of cefepime surpasses those of ceftazidime and cefotaxime [9,10]. Furthermore, many derepressed mutants of *Enterobacter cloacae, Citrobacter freundii, Serratia marcescens, Pseudomonas aeruginosa*, and other members of the family *Enterobacteriaceae* which are resistant to cefotaxime and ceftazidime remain susceptible to cefepime [2,11]. Therefore, cefepime appears to be a promising and suitable agent for the treatment of patients with severe infections, including those patients with nosocomial infection due to various pathogens. Although there have been reports on the efficacy and safety of cefepime in the treatment of various infections in Western countries [3-5], cefepime has only recently been introduced into clinical use in Taiwan and only minimal experience involving a small number of cases in Taiwan has been reported. In this study, we reviewed the demographic data, clinical features, microbiological

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results, adverse effects, and final outcomes of all hospitalized patients who received cefepime treatment at our hospital during a 4-month period from January to April 1999 and evaluated the efficacy and safety of cefepime in the treatment of serious infections.

Patients and Methods

During the period from January 1999 to April 1999, all adult hospitalized patients (including patients in the emergency service, intensive care units, and general wards) who had severe bacterial infections and received a regimen containing cefepime for more than 72 h were included in this study. Cefepime 1 g was given intravenously every 12 h to all patients with normal renal function and the dosage was adjusted according to subsequent assessment of renal function of the patients. Demographic data including age, sex, epidemiological data, underlying medical illness, immunosuppressive factors of hosts, ward of admission and cefepime usage were recorded on a standard record form. Sepsis syndrome criteria [12] and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [13] were obtained at the time of cefepime treatment to estimate the seriousness of infection. Sepsis was defined as clinical evidence of infection plus at least two of the following systemic inflammatory responses: 1. oral temperature of ≥ 38 °C or ≤ 36 °C; 2. respiratory rate of ≥ 20 breaths/min or $PaCO_2$ of ≤ 32 torr; 3. heart rate of ≥ 90 beats/min; 4. blood leukocyte count ≥ 12000 per μL or ≤ 4000 per μL or band form leukocyte $\geq 10\%$ [16]. Nosocomial infection was defined according to the Centers for Disease Control and Prevention definition [14]. Clinical manifestations, sites of infection, initial leukocyte count, indications for cefepime usage, concomitant antibiotic regimens, blood biochemistry results, microbiological results, adverse reactions to cefepime, treatment duration, surgical intervention, and complications were also recorded. The clinical and microbiological responses were evaluated at the end of therapy. The clinical responses were classified as satisfactory: all clinical signs and symptoms relevant to the infection were resolved or improved and no new symptoms was present at post-treatment follow-up; failed: persistence or worsening of clinical signs or symptoms compared to the pretreatment status of infection, discontinuation of drugs due to adverse effects, new microbial superinfection, or death; and unable to determine: no follow-up evaluation of clinical signs and symptoms.

Pathogens were defined as microorganisms isolated from blood, other sterile sites (such as ascites or pleural effusion), and from abscesses or pus from debrided tissues obtained by surgery or aspiration. Isolates from good qualified sputum specimens were considered significant if radiographic study showed obvious consolidation or infiltration in the lungs, and no other concomitant pathogens were identified in the specimen. Bacteria cultured from contaminated specimens such as sputum without concomitant radiographic evidence of consolidation or swab cultures of cutaneous wounds were excluded. The species of isolates were identified by a conventional method [15] and using the Vitek AutoMicrobic System (BioMerieux Vitek, Hazelwood, MO, USA). An assessment of the microbiological response was classified as eradication of the causative microorganism: all cultures done after the completion of therapy were negative; presumed eradication: improved condition but no following culture available because of diminished sputum production, lack of purulent material, or healing of the infection site; persistent infection: if the pretherapy causative pathogen was present during treatment or reappeared after the termination of treatment; and superinfection: a new pathogen was identified and the symptoms of infection continued during the treatment. When the pre-treatment culture was negative, the infection was considered only clinically documented. Death due to bacterial or fungal infections was defined if the patient died of septicemia or sepsis syndrome with significant microbiological or clinical evidences and no other medical condition could be attributed. The significance of differences in clinical and laboratory parameters between patients who received cefepime with or without aminoglycosides therapy was analyzed by chi-square test. A p value less than 0.05 was considered statistically significant.

Results

During the 4-month study period, a total of 55 hospitalized adult patients (32 males and 23 females) had severe bacterial infections and received cefepime therapy for more than 72 h. Their ages ranged from 16 to 94 years with a median of 67 years. Fifty-four of these patients had underlying medical illnesses including malignancy (27 patients), congestive heart failure (16), diabetes mellitus (15), cerebrovascular accident (11), liver cirrhosis (10), uremia (10), chronic lung disease (7), and alcoholism (3). The types of malignancies in these 27 patients included lymphoma or leukemia (7), lung cancer (4), gastric cancer (4), hepatocellular carcinoma (3), cholangiocarcinoma (2), metastatic cancer of unknown origin (2), and cancers of the pancreas (1), kidney (1), rectum (1), nasopharynx (1), and esophagus (1). The immunosuppressive factors predisposing patients to the development of infections

included recent operation (16), postchemotherapy (17), neutropenia (8), and long-term immunosuppressive therapy (5). The clinical characteristics of the patients are shown in table 1.

The etiology and severity of sepsis and treatment duration of the patients are summarized in table 2. Twenty-four of the infections (44%) were community-acquired. Cefepime was commonly used in the intensive care units (44%) and hemato-oncology wards (22%). All but one of the patients had sepsis syndrome. The mean APACHE II score was 18, ranging from 6 to 26. Lung was the most common site of infection (27 patients). The other sites of infection were intra-abdomen (15), skin and soft tissue (8), intravascular device (3), and urinary tract (1). No obvious infection sites were found in four neutropenic patients (blood neutrophil count less than 500/μL) after chemotherapy and one patient who had fever of unknown origin after surgery. Causative microorganisms were isolated in a total of 42 patients from specimens including sputum (in 18 patients), blood (16), surgical drainage of abscesses or aspiration of pus (12), catheter tips (3), bile (3), ascites (2), and urine (1). The most commonly isolated bacteria were *P. aeruginosa* (23), *E. cloacae* (21), *Klebsiella pneumoniae* (7), *Escherichia coli* (6), *Acinetobacter baumannii* (4), and *S. marcescens* (3). Mixed infections were found in 16 of the 55 patients. The isolation sites and microbiological results are shown in table 3.

The mean duration of cefepime therapy was 13 days with a range of 3 to 42 days. Concomitant antimicrobial agents were used in 34 patients including aminoglycosides (30 patients), vancomycin (5), and metronidazole (5). The major indications for cefepime therapy were positive cultures with drug sensitivity results (29), failure of other antimicrobial therapy regimens(18), empirical therapy for febrile neutropenia (4), and severe immunocompromise (4). An infectious disease specialist was consulted before cefepime use in 36 of the patients, while 19 did not receive consultation.

Table 1. Clinical characteristics of 55 hospitalized patients with severe infection who received cefepime therapy

Demographic data	No. of patients (%)
Sex, ratio of males/females	32/23 (60/40)
Mean age, y, (range)	67 (16-94)
Underlying diseases	
Malignancy[a]	27 (49)
Congestive heart failure	16 (29)
Diabetes mellitus	15 (27)
Cerebrovascular accident	11 (20)
Liver cirrhosis	10 (18)
Uremia under dialysis	10 (18)
Chronic lung diseases	7 (13)
Alcoholism	3 (5)
Host immunocompromised risk factors	
Recent operation	16 (29)
Post-chemotherapy	17 (31)
Neutropenia[b]	8 (15)
Immunosuppressive therapy	5 (9)
Burn	2 (4)
Blood leukocyte count per μL (range)	12150 (70-26720)

[a]Including solid tumor (20 patients) and hematological malignancy (7).
[b]Neutropenia was defined as a blood neutrophil count less than 500 per μL.

Table 2. Etiology, severity, clinical sepsis syndromes, and treatment duration of 55 hospitalized patients with cefepime therapy

Category	No. of patients (%)
Etiology	
Community-acquired infection	24 (44)
Nosocomial infection	31 (56)
Wards which used cefepime	
Emergency department	2 (4)
Intensive care units	24 (44)
General wards[a]	29 (52)
Sepsis syndrome[b]	54 (98)
Mean APACHE II score (range)	18 (6-26)
Clinical syndrome	
Pneumonia[c]	27 (49)
Intra-abdominal infection[d]	15 (27)
Skin and soft tissue infection[e]	8 (15)
Febrile neutropenia	4 (7)
Intravascular device-related infection	3 (5)
Others[f]	2 (4)
Mean treatment duration, days (range)	13 (3-42)

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II
[a]Including hemato-oncology ward (12), medical wards (10), and surgical wards (7).
[b]Including septic shock (17 patients), multiple organ failure syndrome (8), acute respiratory distress syndrome (6), and disseminated intravascular coagulation (4).
[c]Community-acquired pneumonia (9 patients) and nosocomial pneumonia (18).
[d]Including peritonitis (4 patients), liver abscess (3), necrotizing cholecystitis (3), cholangitis (3), and pancreatic abscess (2).
[e]Surgical wound infection (2 patients), burn wound infection (2), diabetic foot infection (2), cellulitis (1), and necrotizing fasciitis (1).
[f]Including urinary tract infection (one patient) and fever of unknown origin (1).

Table 3. Microbiological features of 55 patients with severe infection who were treated with cefepime

	No. of isolates
Isolation sites	
Blood	16
Pus from debrided tissue or abscess	12
Purulent sputum	18
Others[a]	9
Causative microorganisms (eradication rate, %)	
Pseudomonas aeruginosa	23 (87)
Enterobacter cloacae	21 (100)
Klebsiella pneumoniae	7 (100)
Escherichia coli	6 (100)
Acinetobacter baumannii	4 (0)
Serratia marcescens	3 (33)
Others[b]	12 (92)

[a]Including catheter tip (3 isolates), ascites (2), bile (3), and urine (1).
[b]Including *Burkholderia cepacia* (2 isolates), *Morganella morganii* (2), *Staphylococcus aureus* (2), *Enterococcus faecium* (2), *Citrobacter freundii* (1), *Eikenella corrodens* (1), *Streptococcus intermedius* (1), and Group F *Streptococcus* (1), all but one case of *Citrobacter freundii* were successfully eradicated by cefepime.

The clinical and microbiological outcomes of the patients are shown in table 4. Treatment was successful in 31 patients, four failed to respond to cefepime treatment but were successfully treated after changing to other antimicrobials due to superinfection (3) and drug adverse effects (1). Twenty patients died because of either persistent infection (8), superinfection (7), or underlying disease (5). Among them, four patients died after 2 weeks of cefepime therapy due to either persistent infection (2), superinfection (1), or underlying disease (1). Microbial eradication was documented in 17 patients, and was presumed to be eradicated in seven patients. Persistent microbial infection and superinfection were found in 18 cases. *A. baumannii* (4) and *P. aeruginosa* (3) were the most common persistent pathogens at the infection sites, and *A. baumannii* (4) and fungi (4) were the most common pathogens causing superinfections. Cefepime treatment failed in all four patients with *A. baumannii* infection even though the *in vitro* susceptibility test of the isolates showed susceptibility to cefepime.

Among the 30 patients who received cefepime plus an aminoglycoside, 18 were successfully treated and the causative microorganism was eradicated or presumed-eradicated in 15 out of 23 patients who had a documented pathogen. As to the 25 patients who did not receive aminoglycoside combination therapy, 13 were successfully treated clinically and the causative microorganism was eradicated or presumed-eradicated in nine patients out of 19 patients who had documented pathogens. There was no significant difference in the clinical response rate ($p = 0.63$) and microbial

Table 4. Microbiological and final clinical outcomes of 55 hospitalized patients with severe infection treated with cefepime therapy[a]

	Total (n = 55)	Cefepime without aminoglycoside therapy (n = 25)	Cefepime combined with aminoglycoside therapy (n = 30)	*p*
Clinical outcomes (%)				
Satisfactory response	31 (58)	13 (52)	18 (60)	0.63
Failed and change drugs	4 (7)	2 (8)	2 (7)	
Superinfection	3	2	1	
Adverse effect[b]	1	0	1	
Death	20 (36)	10 (40)	10 (33)	
Died of persistent infection	8	5	3	
Died of underlying diseases[c]	5	2	3	
Died of superinfection	7	3	4	
Microbiological outcomes (%)				
Eradication	17 (40)	7 (37)	10 (43)	0.25
Presumed eradication	7 (17)	2 (11)	5 (22)	
Persistent infection[d]	8 (19)	5 (26)	3 (13)	
Microbial superinfection[e]	10 (24)	5 (26)	5 (22)	
No pathogen found	13	6	7	

[a]Clinical and bacteriological responses of patients treated with cefepime with or without aminoglycosides are shown in the right column.
[b]Patients developed severe leukopenia.
[c]Including advanced malignancies (2 patients), intractable heart failure (2), and chronic lung disease with respiratory failure (1).
[d]Pathogens in cases of persistent infection included *Acinetobacter baumannii* (4), *Pseudomonas aeruginosa* (3), *Serratia marcescens* (2), and *Citrobacter freundii* (1).
[e]Pathogens of superinfection included *Acinetobacter baumannii* (4), *Citrobacter freundii* (1), *Stenotrophomonas maltophilia* (1), and fungi (4).

eradication rate ($p = 0.25$) between the two treatment groups (Table 4).

Six patients developed adverse effects, including eosinophilia (3), leukopenia (2), skin rash (1), and drug-related fever (1). The adverse effects were mild and transient and all of the patients completed their therapy regimens, except for two patients who discontinued cefepime therapy after developing leukopenia and leukopenia with skin rashes after 28 and 9 days of cefepime therapy, respectively. The leukocyte count of these two patients recovered to normal after 13 and 5 days of discontinuation of cefepime, respectively. All noted adverse effects subsided quickly after completion of cefepime therapy.

Discussion

Since the introduction and extended usage of many third-generation cephalosporins in the 1980s, several newly developed resistance mechanisms in various gram-negative bacteria have appeared, such as the derepressed Amp C enzymes produced by *Enterobacter* species and *C. freundii*, and the extended spectrum ß-lactamases (ESBL) produced by *K. pneumoniae* and *E. coli*. These emerging mechanisms of antimicrobial resistance have compromised the effectiveness of the ß-lactams. Cefepime is a newly developed fourth-generation cephalosporin with an extended-spectrum of activity against many gram-positive bacteria, including *Streptococcus pneumoniae* and *Staphylococcus aureus*, and gram-negative organisms, including multi-resistant gram-negative bacteria such as *Enterobacter* and *Klebsiella* species carrying Bush group 1 ß-lactamase [16]. Furthermore, cefepime has activity comparable to ceftazidime against *P. aeruginosa*, even though this organism is resistant to other cephalosporins and aminoglycosides [17,18]. Therefore, it is reasonable to regard cefepime as a good alternative agent for the treatment of nosocomial infections and most serious community-acquired infections in hospitalized patients [19,20].

Several studies have demonstrated excellent clinical efficacy and microbiologic eradication rates with cefepime treatment for febrile neutropenia [1,3], pneumonia [21], skin and soft tissue infection [22], and sepsis syndrome [2,5,9]. In the present study, we also found that cefepime is effective in treatment of serious infections. The present study demonstrates the efficacy of cefepime across a more diverse disease spectrum than previous studies [9-11,23] and the patients in this series also had more serious conditions, including those complicated with sepsis. The mean value of APACHE II score was 18. Sepsis was complicated with shock in 31% of patients and with multiple organ failure syndrome in 15%. Most of our patients had underlying medical illness and had immunocompromised conditions, such as elderly, malignancy, recent operation, postchemotherapy, diabetes, uremia, chronic lung disease, or liver disease which could exacerbate the infection.

Cefepime has been demonstrated to have very good *in vitro* activity against *P. aeruginosa* [17,23]. In this study, cefepime treatment had better results against *P. aeruginosa* than that in previous studies, with a much lower failure rate (13% versus 30-40%) [3,17,23]. Previous studies also showed that *Enterobacter* species which had reduced susceptibility or resistance to ceftazidime and other ß-lactam drugs, were susceptible and responded clinically to cefepime [24,25]. Compatible with those results, the *E. cloacae* infections and all other *Enterobacteriaceae* infections in the present series were all successfully treated. Concomitant antimicrobial therapy was administered in 62% of patients, and near 90% of these patients received aminoglycosides. Although we did not find the benefits of combination therapy with aminoglycosides in the present study, an *in vitro* synergy has been demonstrated against *P. aeruginosa, S. marcescens*, and *B. cepacia* when cefepime was combined with an aminoglycoside. Therefore, it is understandable why so many patients received combination therapy [18].

The clinical response rate and bacteriologic eradication rate in the present study (58% and 57%, respectively) were much lower than in previous series [26,27]. The main reasons for this finding include that our patients were at higher risk for the development of severe infection, with more serious conditions and complications, and that most patients stayed in the intensive care units and hematology-oncology wards, where superinfection or death due to pre-existing disease were very common. Thus, differences in patient selection among these studies make comparison difficult. We found that cefepime had poor effectiveness in treating *A. baumannii* and *S. marcescens* infections, and several patients acquired secondary infections due to *A. baumannii* and fungi. Clinicians should be alert to the possibility of superinfection caused by these microorganisms if a patient fails to respond to the treatment with cefepime after several days.

In this study, cefepime was found to be well tolerated in Taiwanese patients. All of the adverse effects encountered in our patients were mild and transient, and only two of them discontinued the drug due to leukopenia. None of the abnormal laboratory values found in our patients was clinically relevant, and all of

these values returned to normal levels after treatment was completed or discontinued. In conclusion, the results of this study demonstrate that cefepime is effective and safe for the treatment of serious bacterial infections in hospitalized patients in Taiwan.

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