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ORIGINAL WORK

Clinical, Electroencephalographic Features and Prognostic Factors of Cefepime-Induced Neurotoxicity: A Retrospective Study

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Abstract

Background: The incidence of cefepime-induced neurotoxicity (CIN) has been previously underestimated, and there have only been sporadic reports from critical neurological settings. The present study aimed to investigate the potential factors associated with disease development, electroencephalography (EEG) sub-classification, and outcome measures.

Methods: The 10-year medical records of patients who underwent EEG between 2007 and 2016 at a tertiary medical center in Taiwan, and developed encephalopathy after cefepime therapy were retrospectively reviewed. Age- and sex-matched controls were included for further analysis. Demographic data, the occurrence of clinical seizures, non-convulsive status epilepticus (NCSE), use of antiepileptic drugs (AEDs), receiving maintenance or urgent hemodialysis, EEG findings, and functional outcomes were analyzed. The Chi-square test and a logistic regression model were applied to survey significant prognostic factors relating to mortality.

Results: A total of 42 CIN patients were identified, including 25 patients from wards and 17 from intensive care units; their mean age was 75.8 ± 11.8 years. Twenty-one patients (50%) had chronic kidney disease, and 18 (43%) had acute kidney injury. Among these patients, 32 (76%) received appropriate cefepime dose adjustment. Three patients had a normal renal function at the time of CIN onset. The logistic regression model suggested that maintenance hemodialysis and longer duration of cefepime use were independently associated with the development of CIN, with odds ratios of 3.8 and 1.2, respectively. NCSE was frequently noted in the CIN patients (64%). Generalized periodic discharge with or without triphasic morphology was the most common EEG pattern (38%), followed by generalized rhythmic delta activity and generalized spike-and-waves. AEDs were administered to 86% of the patients. A total of 17 patients (40%) did not survive to hospital discharge. Adequate cefepime dose adjustment and early cefepime discontinuation led to a better prognosis.

Conclusions: CIN was associated with high mortality and morbidity rates. Neurotoxic symptoms could still occur when the cefepime dose was adjusted, or in patients with normal renal function. Patients with maintenance hemodialysis or a longer duration of cefepime therapy tended to develop CIN. Early recognition of abnormal EEG findings allowed for the withdrawal of the offending agent, resulting in clinical improvements and a better prognosis at discharge.

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Keywords: Cefepime neurotoxicity, Encephalopathy, Periodic discharges, Prognostic factor, Hemodialysis

Introduction

Penicillin-induced neurotoxicity has been well known for decades [1]. Accumulating evidence has shown that the majority of beta-lactam antibiotics including cephalosporins and penicillin are associated with neurotoxicity and convulsions due to their antagonistic effect on the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) receptor [2]. Cefepime is a fourth-generation cephalosporin, with a primary structure including a six-membered thiazolidine ring fused to the beta-lactam portion, and a 7-aminocephalosporanic acid nucleus [3]. Due to its extended spectrum of activity, cefepime is usually reserved to treat severe nosocomial pneumonia, systemic infections which are caused by multi-resistant microorganisms (e.g., *Pseudomonas aeruginosa*), and for the empirical treatment of febrile neutropenia [4]. Cefepime can also penetrate the central nervous system (CNS) and be used to treat bacterial meningitis. Due to its linear pharmacokinetic profile and predominantly renal clearance characteristics, patients with renal insufficiency tend to have a longer elimination half-life and decreased total body clearance [5, 6]. Cefepime can therefore accumulate in both the blood and cerebrospinal fluid (CSF) [7, 8], and in vivo and in vitro models have shown that high CSF cefepime concentrations can reduce the seizure threshold and provoke neuronal excitability via blocking inhibitory effects mediated by GABA [2].

Clinically, when cefepime is administered to patients with impaired renal function, cefepime-induced neurotoxicity (CIN) is an essential differential diagnosis if patients develop an altered conscious level, myoclonus, convulsive seizures, or non-convulsive status epilepticus (NCSE) with continuous epileptiform discharges on electroencephalography (EEG) [4, 9–19]. The incidence of CIN has been reported to range between 1 and 15% [12, 20]. Two recent systematic review studies reported that 44% of patients with CIN were intensive care unit (ICU) patients, and that the mortality rate was 13% [21, 22]. Another retrospective study reported a higher 30-day mortality rate of up to 42.8% [23]. In addition, approximately 80% of the patients in the two recent systemic review studies had EEG studies, which showed that 25 to 31% of the patients had NCSE [21, 22]. As CIN may occur at any age and in those with any underlying disease, immediate EEG studies are an essential method for the early detection of abnormal signs and the prompt management of CIN. Previous studies have suggested that in addition to discontinuing cefepime treatment, urgent hemodialysis and antiepileptic drugs (AEDs) should be considered to reverse the condition [8, 12, 24]. Clinical improvements were observed in a median of 2 days after these interventions in one study [22].

CIN is of particular concern to both physicians and families when it develops in critically ill patients, and questions regarding the functional outcome are frequently encountered. The objectives of this study were to perform a case–control cohort study to investigate the clinical factors associated with the development of CIN, EEG characteristics, outcome measures, and potentially reversible effects after urgent hemodialysis and AED treatment.

Methods

Isolation of Eligible Study Subjects and Standard Protocol Approval

We conducted this retrospective case-matched observational study at Chang Gung Memorial Hospital (Linkou, Taiwan), which is a tertiary medical center. Information from the hospital's medical database on patients treated with cefepime during a 10-year period (January 1, 2007, through December 31, 2016) was retrospectively reviewed. During this period, we cross-linked data from our EEG database to identify in-hospital patients who presented with rhythmic or periodic patterns on their EEG while taking cefepime. We also included age- and sex-matched patients at a 1:1 ratio as a control group, who received cefepime during the same study period but did not develop symptoms of CIN. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (201801183B0C601).

Inclusion/Exclusion Criteria

Medical records of the enrolled cases were reviewed. Patients who received intravenous cefepime within 14 days prior to the onset of new neurologic symptoms, and had received at least 3 days of cefepime treatment were included [13]. A diagnosis of CIN required the following criteria to be met: (1) patients who developed neurologic symptoms consistent with encephalopathy, including altered consciousness or mental changes, seizures, or myoclonus after cefepime administration, with a clear temporal association between the neurological symptoms and the administration of cefepime [12]; (2) patients with clinical or EEG improvements after the discontinuation of cefepime; and (3) cefepime therapy was the only identified cause of the patient's

neurological symptoms. Patients with other factors (not including cefepime treatment) contributing to their neurological symptoms were excluded from the study.

Demographic and EEG Data Collection

The management procedures and clinical outcomes were obtained from the patient's medical records. Demographic data, cefepime usage profiles, baseline laboratory data including renal, liver and nutritional status, whether or not hemodialysis was performed during cefepime treatment, neurological profiles, and clinical outcomes at hospital discharge were collected and evaluated. An adjustment in the dose of cefepime for renal function was considered to be appropriate according to the online Micromedex® 2.0 database. The patients were classified into ward and ICU groups for further analysis.

EEG recordings were obtained using the 10–20 international system of electrode placement. The specific EEG characteristics in our cohort were categorized according to the American Clinical Neurophysiology Society 2012 terminology [25], including lateralized periodic discharges (LPDs), bilateral independent periodic discharges (BIPDs), generalized periodic discharges (GPDs) with and without triphasic morphology, generalized rhythmic delta activity (GRDA), lateralized rhythmic delta activity (LRDA), lateralized spike-and-waves (LSWs), generalized spike-and-waves (GSWs), and multifocal spike-and-waves (MfSWs). NCSE was defined as an epileptic condition with abnormal EEG patterns of epileptiform discharges, during which subtle clinical ictal phenomena developed (reduced or altered consciousness and behavioral, vegetative, or merely subjective symptoms, such as auras, but without major convulsive movements, lasting for at least 10 min) [26, 27].

Essential laboratory data associated with metabolic and infectious conditions were recorded, including creatinine, blood urea nitrogen, estimated glomerular filtration rate (eGFR), C-reactive protein, aspartate transaminase, alanine transaminase, albumin, and ammonia. The Cockcroft–Gault formula, a widely used method to predict creatinine clearance, was applied for the calculation of eGFR [28]. Acute kidney injury (AKI) was defined as a 1.5-fold increase in creatinine from baseline or an absolute increase in creatinine by 0.3 mg/dL. Patients were considered to have chronic kidney disease (CKD) if their baseline eGFR was below 60 mL/min/1.73 m^2 for >3 months. For additional prognostic analysis, patients who received hemodialysis, either maintenance or urgent, were divided into separate groups. Hypoalbuminemia was defined as an albumin level below 3.5 g/dL.

Clinical Outcome Measurements

Clinical improvement was defined as either an improvement in conscious level or the resolution of clinical seizures and myoclonus after the discontinuation of cefepime. An improvement in EEG was defined as the disappearance of abnormal EEG activity after cefepime cessation. Early discontinuation was defined as the withdrawal of cefepime within five days after the development of CIN. Functional outcomes at the time of hospital discharge were recorded. The modified Rankin Scale (mRS) was used to determine the outcome measures at hospital discharge [29]. Independence in activities of daily living (ADL) was defined as an mRS score of 0 to 3, while dependence in ADL was defined as an mRS score of 4 or higher at discharge.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline characteristics. Categorical data were presented as number (%), and continuous data were presented as the mean ± standard deviation (SD) or median with the corresponding interquartile range (IQR). Fisher's exact test or the Chi-square test was performed for comparisons between subgroups and categorical variables. Normally distributed continuous variables were compared using the Student's t test, and non-normally distributed continuous variables were compared using the Mann–Whitney U test or Kruskal–Wallis test as appropriate. All positive factors ($P \leq 0.1$) potentially associated with the risk of developing CIN were included in multivariate regression analysis. The magnitude of association was reported as the odds ratio (OR) and corresponding 95% confidence interval (CI). Receiver operating characteristic (ROC) curve analysis was also performed, and the area under the curve (AUC) was calculated. $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Demographic Data of the CIN and Control Groups

During the study period, a total of 15425 patients were treated with cefepime, among whom 42 (29 females [69%] and 13 males [31%]; mean age, 75.8 ± 11.8 years) who fulfilled the criteria of CIN were recruited into the present study. Thus, the incidence rate of CIN was around 0.27% in our cohort. Forty-two age- and sex-matched control patients were also included for further analysis (Table 1).

The preexisting comorbidities of the patients in the CIN and control groups are listed in Table 1. There were no significant differences in any preexisting comorbidity. Regarding the renal status in the CIN group, the median

Table 1 Baseline characteristics of the CIN cases and controls

Characteristics	CIN Cases ($n=42$)	Controls ($n=42$)	*P* value
Age, years, mean ± SD	75.8 ± 11.8	73.1 ± 11.6	0.28
Female, n (%)	29 (69)	29 (69)	1.00
Preexisting comorbidities, n (%)			
Cerebrovascular accident	10 (24)	8 (19)	0.60
Ischemic heart disease	4 (10)	8 (19)	0.21
Diabetes mellitus	19 (45)	11 (26)	0.06
Arterial hypertension	27 (64)	18 (43)	0.05
Chronic respiratory disease	16 (38)	12 (29)	0.36
Renal condition at CIN onset, n (%)			
eGFR, median (IQR)	22.4 (9.3–51.5)	42.5 (13.3–94.8)	0.02
Acute kidney injury	18 (43)	16 (38)	0.66
Chronic renal dysfunction	21 (50)	14 (33)	0.12
Maintenance hemodialysis	12 (29)	5 (12)	0.06

CIN, cefepime-induced encephalopathy; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation

eGFR was 22.4 mL/min/1.73 m^2, compared to 42.5 mL/min/1.73 m^2 in the controls ($P=0.02$). Of the 42 patients, 18 (43%) had AKI and 21 (50%) had CKD on admission, and 12 received maintenance hemodialysis. Three patients with normal renal function developed CIN following cefepime treatment.

The Dosing and Duration of Cefepime Usage

The dosing and duration of cefepime usage of the patients in the CIN and control groups are listed in Table 2. There was no significant difference in daily dose of cefepime between the two groups. However, there were significant differences in appropriate dose adjustment (76% vs. 100%, $P=0.001$) and median usage duration (10 vs. 5 days, $P<0.001$) between the CIN and control groups. In the CIN group, the patients developed CIN symptoms at an average of 4 days (range 1–6 days) after cefepime use. All patients received an EEG study after a median of 8 days (range 6–12 days). The median cefepime discontinuation time was 4 days, with 86% of the patients discontinuing treatment early within 5 days.

Clinical and Electroencephalographic Features of CIN

The patients' neurological symptoms and EEG characteristics are summarized below. Clinical seizures were recorded in 15 patients (36%), including focal seizures in three, complex partial seizures in two, and generalized tonic–clonic seizures in 10. NCSE was recorded in 27 patients (64%) and myoclonus in 10 (24%). All patients had abnormal EEG findings (Fig. 1), including LPDs in four (9%), BIPDs in three (7%), GPDs with or without triphasic morphology in 16 (38%), GRDA in 11 (26%), LSWs in two (5%), GSWs in four (10%), and MfSWs in two (5%). GPD was the most frequently encountered EEG pattern in our cohort, followed by GRDA and GSWs. Figure 2 demonstrates two sample cases who had clinical symptoms of CIN and specific EEG patterns of periodic discharges after receiving cefepime treatment (Fig. 2).

Outcome Measures of the CIN Patients in the Ward and ICU Cohorts

We further classified all CIN patients into ward and ICU groups in order to evaluate their separate treatment and outcome measures (Table 3). There were 25 patients (60%) in the ward group and 17 patients (40%) in the ICU group. AED treatment was used in 36 patients (86%), including levetiracetam in 20, valproate in 17, phenytoin in 10, midazolam infusion in seven, and oxcarbazepine in one. Thirteen of the patients received urgent hemodialysis due to AKI during the diagnosis of CIN.

Regarding the outcome measures at hospital discharge, the rates of clinical and EEG improvements were similar in both groups. A total of five and 20 patients had

Table 2 The dosing and duration of cefepime usage ($n=42$)

Characteristic	CIN cases ($n=42$)	Controls ($n=42$)	*P* value
Cefepime dose over 24 h, g, mean ± SD	3.5 ± 1.7	3.4 ± 2.0	0.73
Appropriate dose adjustment according to renal function, *n* (%)	32 (76)	42 (100)	0.001
Median usage duration, day (IQR)	10 (7–13)	5 (3–8)	< 0.001
Median onset of neurological symptoms, day (IQR)	4 (1–6)	–	
Median time to EEG study, day (IQR)	8 (6–12)	–	
Median time from symptoms to cefepime discontinuation, day (IQR)	4 (2–10)	–	
Early discontinuation of cefepime, *n* (%)[a]	36 (86)	–	

CIN, cefepime-induced encephalopathy; EEG, electroencephalography; IQR, interquartile range; SD, standard deviation

[a] Withdrawal of cefepime within 5 days after the development of CIN

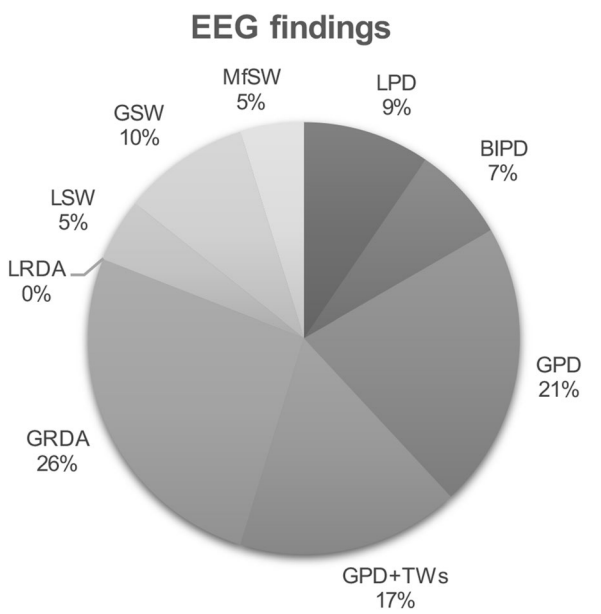

Fig. 1 EEG characteristics of the CIN patients ($N = 42$). All patients were classified into one EEG subtype according to ACNS terminology. GRDA was the most frequent EEG pattern (26%), followed by GPD with or without triphasic waves. None of our patients developed LRDA. EEG, electroencephalography; CIN, cefepime-induced encephalopathy; ACNS, American Clinical Neurophysiology Society; LPD, lateralized periodic discharge; BIPD, bilateral independent periodic discharge; GPD, generalized periodic discharge; TW, triphasic wave; GRDA, generalized rhythmic delta activity; LRDA, lateralized rhythmic delta activity; LSW, lateralized spike-and-waves; GSW, generalized spike-and-waves; MfSW, multifocal spike-and-waves

independence and dependence in ADL at hospital discharge, respectively. Seventeen patients did not survive to hospital discharge, leading to a mortality rate of 40.5%. No significant difference was observed in mortality between the two groups (9 vs. 8 patients).

Clinical Variables Associated with Outcomes as Measured at Hospital Discharge

To determine patient outcomes associated with CIN at discharge, the patients were sub-grouped into independence in ADL, dependence in ADL, and mortality groups. Variables including age, baseline renal status, hypoalbuminemia, cefepime usage duration, appropriate cefepime dose adjustment, early discontinuation, maintenance or urgent hemodialysis, seizures, myoclonus, EEG findings, AED use, and clinical and EEG improvements were analyzed (supplemental Table 1). In the patients with non-mortality outcomes at discharge, 19 out of 25 patients (76%) had adequate cefepime dose adjustment and 22 (88%) had early cefepime discontinuation. For those with late discontinuation, three patients died after receiving prolonged cefepime use (> 10 days). Of note, all five patients with independence in ADL had early cefepime discontinuation.

Predicting Model for the Development of CIN

A multivariate logistic regression model was used to identify the factors potentially associated with the risk of developing CIN (Table 4). Factors including renal status, preexisting comorbidities, age, cefepime profile

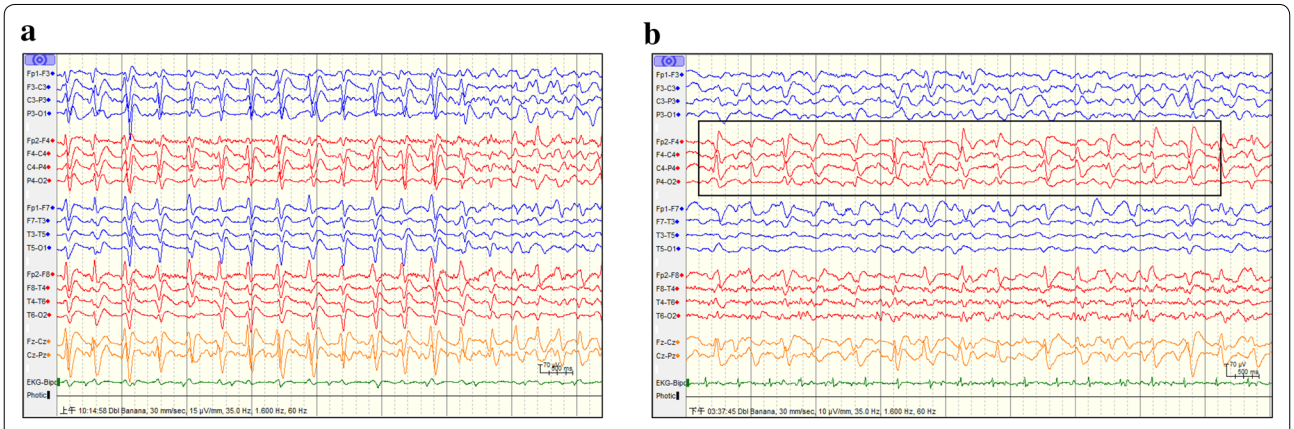

Fig. 2 Sample cases of GPDs and LPDs. **a** A 73-year-old male patient had underlying hepatocellular carcinoma, chronic kidney disease, and hypertension. He was admitted to ICU for treatment of pneumonia. He developed acute altered mental status after cefepime treatment for 5 days. The EEG in bipolar montage showed frequent GPDs with triphasic morphology at a frequency of 2.5–3 per second. The patient's intermittent dull response was regarded as NCSE. He expired due to severe medical condition despite discontinuation of cefepime therapy. **b** An 88-year-old male patient who had acute kidney injury during ICU admission developed focal motor seizures with impaired consciousness after cefepime treatment for 5 days. The EEG in bipolar montage revealed 1–2 sharply contoured LPDs per second over the right frontocentral area. The EEG findings resolved after early drug discontinuation. His consciousness and neurological symptoms also improved with independence in ADL at discharge. ICU, intensive care unit; EEG, electroencephalography; GPDs, generalized periodic discharges; NCSE, non-convulsive status epilepticus; LPDs, lateralized periodic discharges; ADL, activity of daily living

Table 3 Treatment and outcome measures of CIN patients in wards and ICU

	Ward patients ($n=25$)	ICU patients ($n=17$)	*P* value
Treatment, n (%)			
Antiepileptic drug use	22 (88)	14 (82)	0.67
Emergent hemodialysis[a]	7 (28)	6 (35)	0.74
Outcomes, n (%)			
Resolution of neurological symptoms	14 (56)	7 (41)	0.53
Resolution of EEG abnormalities	19 (76)	14 (82)	0.72
Survived, independence in ADL (mRS 0-3)[b]	3 (12)	2 (12)	1.00
Survived, dependence in ADL (mRS 4-5)[b]	13 (52)	7 (41)	0.54
Mortality	9 (36)	8 (47)	0.53

ADL, activity of daily living; CIN, cefepime-induced neurotoxicity; ICU, intensive care unit; mRS, modified Rankin Scale

[a] Excluding patients who received maintenance hemodialysis

[b] Best mRS at hospital discharge

Table 4 Odds ratios of the development of CIN according to clinical factors

	Univariate analysis			Multivariate analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
eGFR	0.03	0.99	(0.97–0.99)	0.44	0.99	(0.98–1.0)
Acute kidney injury	0.66	1.22	(0.51–2.92)			
Chronic renal dysfunction	0.12	2.00	(0.83–4.83)			
Maintenance hemodialysis	0.06	2.96	(0.94–9.34)	0.05	3.80	(0.96–15.02)
Cerebrovascular accident	0.60	1.33	(0.46–3.79)			
Ischemic heart disease	0.22	0.45	(0.12–1.62)			
Diabetes mellitus	0.07	2.33	(0.93–5.83)	0.35	1.76	(0.54–5.79)
Arterial hypertension	0.05	2.40	(0.99–5.78)	0.62	1.34	(0.42–4.24)
Chronic respiratory disease	0.36	1.54	(0.62–3.84)			
Age	0.28	1.02	(0.98–1.06)			
Cefepime dose	0.72	1.00				
Duration of cefepime use	0.001	1.18	(1.07–1.31)	0.002	1.20	(1.07–1.34)
Appropriate dose adjustment	1.00	0.00				

CI, confidence interval; CIN, cefepime-induced neurotoxicity; eGFR, estimated glomerular filtration rate; OR, odds ratio

(dose, duration, and appropriate dose adjustment) were included in univariate analysis. The multivariate model indicated that maintenance hemodialysis (OR 3.8 [95% CI 0.96–15.02], $P=0.05$) and the duration of cefepime therapy [OR 1.2 (95% CI 1.07–1.34), $P=0.002$] were potential predictors of the development of CIN. We then tested the ROC curve between the duration of cefepime therapy and the development of CIN. The results showed an AUC of 0.787 ($P<0.001$), suggesting that a longer duration of cefepime therapy was a potential indicator for the development of CIN.

Discussion

The current study reviewed 10 years of data from a tertiary medical center on patients cared for in general wards and the ICU who received cefepime during hospitalization. The most important finding was that the patients who received maintenance hemodialysis and had a longer duration of cefepime therapy tended to develop CIN. In the CIN patients, adequate cefepime dose adjustment and early cefepime discontinuation led to a better prognosis. In EEG sub-classification, GPD with or without triphasic morphology was the most frequently encountered EEG pattern in the CIN patients.

The average time from the administration of cefepime to the development of CIN was 4 days (range 1–6 days). However, a gap (with a mean duration of 4 days) was observed between the development of CNS symptoms and cefepime discontinuation. This may be because the physicians were not aware of CIN, as more than half of the patients did not exhibit positive neurological signs. In addition, the similarities in the duration of cefepime therapy and time to EEG studies indicated that most

of the physicians were aware of this diagnosis once an abnormal EEG pattern had been observed.

EEG patterns that fall along the ictal-interictal continuum (IIC) include rhythmic delta activity, periodic discharges, and spikes or sharp waves [30, 31]. These distinct EEG findings are frequently encountered in critically ill patients or following acute brain injury and have been associated with electrographic seizures and poor outcomes [30–34]. Continuous EEG recording is often required to better clarify specific characteristics, such as pattern frequency, plus modifiers, prevalence, and stimulation-induced patterns [30, 32, 35, 36]. GPDs have been strongly associated with convulsive seizures with plus modifiers or faster frequency, whereas GRDA has not [32]. In addition, non-convulsive seizures and NCSE are more frequently noted in critically ill patients with GPDs compared to controls [37]. Many previous studies have reported continuous generalized rhythmic sharp-and-slow wave complexes, GPDs, GRDA, biphasic sharp waves, semi-periodic diffuse triphasic waves, and stimulus-induced rhythmic, periodic, or ictal discharges in CIN patients [9, 23, 38–41]. GPDs, GRDA, and multifocal sharp waves were also the most common EEG patterns observed in the present study after the administration of cefepime, indicating the likelihood of convulsive seizures or NCSE. An interesting finding was that several patients had focal seizures or EEG findings of LPDs, which suggests the possibility of EEG lateralization in CIN patients. According to a literature review, no similar results have previously been reported. Several treatment algorithms and strategies have been proposed for the management of patients with IIC, all of which emphasized the essential role of AEDs and anesthetic medications [31, 42, 43]. There was also a high rate of AED usage (up to 86%) in the present study, although this was not directly related to the final prognosis.

Most CIN patients developed either dependence in ADL or mortality at hospital discharge. We previously reported that CIN is an independent risk factor for mortality in patients with periodic discharges [44]. In the present study, an overall mortality rate of 40.5% was observed in the patients with CIN, which is comparable to a previous study [23]. For CIN patients, withdrawal of the offending drug has been shown to have a more critical effect than the administration of AEDs or anesthetic medications [45]. This reversible phenomenon was also consistent with our data, as 88% of the patients with a non-mortality outcome (100% in the independence in ADL group) discontinued cefepime early. For the patients with late discontinuation (>10 days), there was a tendency toward a worse outcome. These results emphasize the importance of early discontinuation (within 5 days) in CIN patients.

Critically ill patients with acute or chronic kidney disease without an adjustment in the dosage of cefepime have been reported to be particularly susceptible to cefepime neurotoxicity [8, 12, 41, 46–48]. Previous studies have also reported that renal replacement therapy, hemodialysis or high-volume continuous venovenous hemofiltration therapy and monitoring of plasma cefepime levels are necessary to reverse this lethal neurological condition [6–8, 46, 47, 49]. In the current study, we found that the patients with maintenance hemodialysis and a longer duration of cefepime therapy had a tendency to develop CIN (ORs of 3.8 and 1.2, respectively). Therefore, we suggest shortening the cefepime treatment course in a clinical setting once the critical infection has been controlled.

We also found a close relationship between abnormal renal function and CIN in the present study, with 93% of patients having abnormal renal function, either AKI or CKD, of whom half required maintenance hemodialysis. Although 76% of the patients with impaired renal status had an appropriate adjustment in the dose of cefepime according to their renal function, they still developed CIN. There are two possible explanations. First, according to a previous report, inappropriate pharmacokinetic/pharmacodynamic parameters were frequently noticed in critically ill patients with renal insufficiency despite following standard dose adjustment algorithms [49]. Second, paradoxical results with regards to the development of CIN have been reported in patients with normal renal function [23, 50–54]. This indicates that even in patients with a normal creatinine clearance rate, cefepime should be used with caution in the elderly and those with intracranial pathology, such as chronic white matter ischemic changes. Therefore, we suggest that EEG studies should be conducted in these patients when CIN is clinically suspected.

There are several limitations to this study. First, it was a retrospective study, and therefore, several important factors including adequate cefepime dose adjustment and urgent medication discontinuation upon recognizing the disease could not be controlled. Second, CIN is a specific disorder diagnosed through clinical observation without specific objective markers. As mentioned, therapeutic-drug-level monitoring may be important for CIN; however, testing for serum cefepime concentration was not available at our hospital. Third, despite our careful study design with regards to patient selection, it was not possible to collect every CIN patient, for example, those who developed neurological symptoms after cefepime treatment who did not receive an EEG study during hospitalization. The incidence rate may therefore have been underestimated in our

patients, and the exact incidence rate remains to be elucidated in further prospective studies.

Conclusions

In conclusion, when cefepime is used in a clinical setting, caution needs to be taken in patients with impaired renal function, and those receiving hemodialysis. Even in patients with normal renal clearance, CIN should also be considered as a differential diagnosis if neurological symptoms and EEG abnormalities develop. Earlier recognition of abnormal EEG patterns with altered levels of consciousness can result in a better clinical prognosis via the prompt discontinuation of cefepime. In addition, the patients in this study who exhibited clinical improvements had a better overall prognosis. The findings of the present study add knowledge to the literature regarding cefepime neurotoxicity. Awareness of the potential neurotoxic clinical manifestations of cefepime and a high degree of vigilance in critically ill patients are essential to identify potentially serious, although reversible, complications of cefepime therapy.

Electronic supplementary material
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Author's contribution
HL contributed to the design, analysis, and interpretation of the data, and drafting of the manuscript for intellectual content. CL contributed to the design and analysis of the data, and revised the manuscript. TW contributed to the design and acquisition of the data. MC, WT, CC, HH, HC, CL, BC, and WL contributed to the interpretation of the data and statistical analysis. SL contributed to the design and conceptualization of the study, the analysis and interpretation of the data, and drafting, revising, and final approval of the manuscript for intellectual content.

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Conflict of interest
The authors declare that they have no conflict of interest.

Ethics Approval and Consent to Participate
This retrospective study was conducted according to the regulations of the institutional review board of the Chang Gung Medical Foundation (201801183B0C601). The ethics committees approved the study protocol and waived the need for informed consent because this observational study did not modify the physician's treatment decisions, and patients' anonymity was guaranteed.

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