Acta Neurologica Belgica
https://doi.org/10.1007/s13760-024-02546-5

REVIEW ARTICLE

Danger in plain sight: determining who is at highest risk for cefepime induced neurotoxicity and its associated morbidity and mortality

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Received: 29 January 2024 / Accepted: 23 March 2024

Abstract
Cefepime is a fourth-generation cephalosporin that is widely used to treat sepsis but is associated with a potentially dangerous neurotoxicity syndrome, cefepime-induced neurotoxicity (CIN). As a result, patients treated with cefepime may be at higher risk for morbidity, including seizures, and mortality. Though the recent ACORN trial concluded that cefepime does not increase the risk of mortality, most of these patients were not critically ill or elderly, two of the most at risk populations for CIN. Further, diagnosis may be difficult in the critical care setting as patients may have multiple reasons for encephalopathy. Therefore, this population in particular should be studied and monitored closely for CIN. Importantly, there are not well defined diagnostic criteria for CIN to guide evaluation and management. Defining the risk factors for CIN and using laboratory and EEG to help support the clinical diagnosis could be helpful in early recognition of CIN to help institute treatment and to rule out seizures. In this mini review, we highlight risk factors for CIN, discuss the possible value of EEG, and propose a diagnostic and management approach in the evaluation and management of CIN.

Keywords Cefepime · EEG · Cefepime-induced neurotoxicity · Encephalopathy · Sepsis

Introduction

Sepsis is a life threatening condition in critically ill patients with risks of morbidity and mortality reaching up to a third of cases [1, 2]. Given the critical importance of early antimicrobial treatment, patients typically receive empirical antibiotics, frequently including cefepime [1, 3]. Cefepime is a broad spectrum, fourth-generation cephalosporin [4] that can penetrate the central nervous system [5], making it an attractive choice for expeditious and broad coverage. Unfortunately, cefepime is associated with a potentially dangerous neurotoxicity syndrome characterized by encephalopathy, hallucinations, myoclonus, clinical and subclinical seizures with high morbidity and mortality: cefepime-induced neurotoxicity (CIN)[6–8].

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Since FDA approval in 1996 and following campaigns for broad spectrum antibiotic treatment of sepsis,[1] cases of CIN are increasingly reported, with multiple reviews and studies assessing the safety and risk of neurotoxicity with cefepime [3–5, 9–12]. Morbidity is high and some suggest that cefepime increases the risk of mortality [4, 8, 13] with an incidence of up to 13–25% [13, 14]. Mortality is more likely in higher risk patients [15]. CIN prolongs the duration of acute encephalopathy and ICU stay, exposing patients to even greater morbidity and mortality [9]. Many studies on CIN vary in the comparators used against cefepime, including ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam, and ceftriaxone [3, 4], but all have a lower risk of mortality [4], and may be alternatives to cefepime depending on the clinical context [13, 15]. Methodologies also differ, though higher quality studies demonstrate higher mortality with cefepime [4]. Though these studies show varying mortality, specific clinical risk factors have been identified that should guide evaluation and treatment.

The Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection (The ACORN Randomized Clinical Trial) is an open-label, parallel-group, randomized comparative safety trial comparing outcomes in adult patients with suspected infection, treated with cefepime

Published online: 08 April 2024

versus piperacillin-tazobactam [3]. The primary outcome was the highest stage of acute kidney injury or death. A secondary outcome was the number of days *alive and free of delirium and coma within 14 days*. In the 2511 patients enrolled, there was no significant difference in kidney injury or death, but patients on cefepime had greater neurological dysfunction: 252 patients (20.8%) on cefepime had coma or delirium compared to 225 patients (17.3%) on piperacillin-tazobactam (absolute difference, 3.4% [95% CI 0.3–6.6%]); hazard ratio for coma or delirium with cefepime was 1.20 (95% CI 1.00 to 1.50) (supplementary 2, eFigure 6 of their study). Most patients on cefepime (54.3%) received treatment for only 3 days (IQR 1–4), and only about one quarter received a 7-day course. Further, the mean ages were 57 and 59 years in the cefepime and piperacillin tazobactam groups, respectively. About 89% of patients in each group were admitted to the hospital ward and ~ 8% to the ICU.

The ACORN study highlights some important points regarding CIN that should be considered when determining the risk of morbidity and mortality using cefepime. The duration of cefepime treatment, patient age, and severity of illness, remain important clinical factors. Most studies of CIN in general are in older patients; for example in one study, median age was 70 years [16]. The elderly are more vulnerable to CIN [14] as conditions such as stroke and Parkinson disease are more common in this population which can increase the risk of adverse neurological events [17]. Further, white matter disease (WMD), more frequent in older patients, is a risk factor for encephalopathy when there are concurrent medical disorders, including CIN [10, 18].

Diagnosing CIN can be difficult in obtunded ICU patients and there may be a delay in identifying encephalopathy and diagnosing CIN thus increasing morbidity and mortality [19]. Sepsis encephalopathy may represent a particular confounder with sepsis encephalopathy reported in up to 36–70% of cases of sepsis [20–22] and it may be difficult to differentiate from CIN. Critically ill patients with septic encephalopathy are at highest risk of CIN, particularly when patients also have renal dysfunction [6, 23]. Septic encephalopathy may be caused by impaired cerebral perfusion, blood brain barrier breakdown, alteration of cerebral autoregulation, microvascular injury, and altered neurotransmission [24], similar factors to those with CIN [14].

The time between onset of CIN and initiation of cefepime is typically 2–6 days [14] and thus a shorter course of treatment similar to those patients in the ACORN study is often used in the emergent setting when patients first arrive to the hospital. Based on sepsis guidelines, antibiotics are often given as single doses in the emergency department, and though the 2nd dose should not be delayed,[25] one should consider the risk factors and tailor antibiotics if possible. This should also be considered when reviewing prior studies of CIN as duration of treatment could itself confound the incidence of CIN and subsequently the risk of morbidity and mortality.

Risk factors for CIN and morbidity and mortality: what are the red flags?

Renal dysfunction and older age (particularly over 65 years) [12] are risk factors for CIN. In 2 meta-analyses of patients with CIN, 80 to 87% had renal dysfunction [14, 16] while most of the patients had a median age of 69 (IQR 54–75). Additionally, a study from our group at Johns Hopkins Hospital and Bayview Medical Center demonstrated an additional association between patients with CIN and preexisting white matter disease (WMD) [10]. In this cohort of cefepime induced triphasic waves, half had either moderate or severe WMD, with 56% of patients with normal renal function having moderate or severe WMD [10]. We hypothesized that WMD may act as a substrate for cefepime encephalopathy with cefepime acting as a "second hit" that leads to CIN [10]. One could consider that WMD is a correlate for older age which is an independent risk factor for CIN but 56% of the cohort was younger than 65 years of age [10] and another study from our group demonstrated that 3/11 patients with WMD-associated TWs were under 65 years of age [18]. Critical illness may also be a risk factor, but studies are lacking comparing critically ill/ICU patients to those admitted to the inpatient medical ward, given that the majority of studies that include patients in the ICU do not have comparators [4, 14]. Table 1 summarizes risk factors for CIN.

The value of EEG in CIN: early diagnosis and ruling out seizures

Avoiding cefepime may not be feasible, but rapid diagnosis and removal of the drug may forestall CIN and avoid missed diagnoses of seizures [10, 13]. Few studies specifically evaluate EEG findings in CIN [5–7, 10, 12, 14, 16, 26, 27] even though EEG could be used as a biomarker for CIN [14]. EEG findings in acute encephalopathy may help in prognosis and expedite diagnosis in critically ill patients [15], leading to clinical and EEG improvement [7, 10, 26]. EEG is particularly valuable in intubated ICU patients where mental status is difficult to assess. EEG in CIN typically reveals

Table 1 Risk factors for CIN

Critical illness
Acute or chronic renal dysfunction
Older age (particularly > 65)
Higher dosing of cefepime
Presence of white matter disease on neuroimaging

evidence of encephalopathy including diffuse slowing, and generalized periodic discharges (GPDs) with ("TWs") and without triphasic morphology. Less frequent findings include lateralized (LPDs) or bilateral independent (BIPDs), focal epileptiform discharges and rarely myoclonic and nonconvulsive status epilepticus [5–7, 14, 26, 27]. In particular, TWs appear to be a prominent finding on EEG in CIN [7, 10, 16]. Some of these EEG patterns lie on the ictal-interictal continuum and patients are at risk of nonconvulsive seizures and status epilepticus which can only be diagnosed with EEG [5–7]. Periodic interictal and ictal patterns may be seen in up to a quarter of cases of CIN monitored with EEG [28, 29] and seizures may be seen in about 10% of cases [30]. Though many of these EEG patterns are protean in evaluating altered mentation, when severe encephalopathic EEG patterns and the ictal-interictal continuum and seizures are encountered there should be strong consideration of removal and replacement of cefepime given the risk in delaying diagnosis and management. Based on published reports and our experience, most patients with CIN have clinical and EEG recovery within a few days of discontinuation of cefepime. Anti-seizure medications are rarely warranted unless clinical or subclinical seizures occur. Continuous video-EEG monitors for intermittent subclinical seizures [27]. The need for EEG monitoring in diagnosing nonconvulsive status epilepticus and the lack of a standardized approach to the evaluation of CIN may impact outcome in CIN [31]. Table 2 summarizes EEG characteristics of CIN.

Recommendations for clinical evaluation

In patients on cefepime without pre-existing encephalopathy, but who then develop progressive altered mentation, the diagnosis is usually straightforward. When neurological deterioration begins within 2–6 days of cefepime, CIN should be strongly considered when clinical investigations fail to provide likely alternate causes, and when fever and other objective evidence of infection regress without improvement in encephalopathy. EEG should be considered in most cases of persistent altered mentation and can confirm encephalopathy and assess the degree of encephalopathy, and exclude nonconvulsive status epilepticus and seizures. If seizures, TWs and other rhythmic and periodic patterns are recorded, cefepime should be discontinued immediately and a different antibiotic with a lower risk of CNS toxicity should be used immediately. Cefepime when used should be at the lowest effective dose, and renal dosing should always be stringently followed; [16] one study showed that 2 g every 12 h is safe in patients with CrCl ≥ 50 ml/min. However, when microbes demonstrate cefepime MICs ≥ 8 mg/l higher dosing may be required with close laboratory monitoring [16] or consideration of alternative antibiotics if overdosing is a risk. Continuous video-EEG monitoring for 24–48 h can help correlate clinical and EEG findings.[34] See Table 3 for proposed evaluations and management in cases of suspected CIN.

Table 2 EEG features of CIN

Generalized periodic discharges with or without triphasic morphology*
Triphasic waves*
Lateralized periodic discharges
Epileptiform discharges and/or seizures
Generalized delta and/or theta slowing

*More specific for CIN in the proper clinical context

Conclusions

Cefepime is widely used to combat sepsis but poses significant risks of CIN and mortality. Though the recent ACORN trial did not demonstrate a higher risk of mortality with using cefepime, their findings cannot be generalized to all patients as sicker, elderly ICU patients were not well represented in the cohort. Older, critically ill patients with and without renal dysfunction are at higher risk of CIN morbidity and perhaps mortality, though patients of any age may be susceptible given the right clinical circumstances including a high dose cefepime treatment and a history of WMD. Though EEG may suggest a nonspecific encephalopathy, the presence of triphasic waves, ictal-interictal rhythmic and periodic patterns and seizures, are supportive of the clinical diagnosis of CIN. A high index of suspicion, presence of risk factors, and the use of EEG and CIN diagnostic criteria can expedite early diagnosis and withdrawal cefepime,

Table 3 Proposed evaluation in cases of suspected CIN

Cefepime therapeutic monitoring (definitely in those with CrCl < 50, otherwise strongly consider)
Pathogenic microbial sensitivity analyses
Consider neuroimaging and other laboratory studies to rule out causes of encephalopathy
EEG as soon as diagnosis is considered based on risk factors and clinical history to rule out seizures
If EEG and/or clinical history consistent with CIN, immediate transition from cefepime to another antibiotic
Consider cEEG monitoring to evaluate for nonconvulsive seizures

which are crucial in avoiding poor outcomes. Future study should focus on critically ill patients and the use of EEG in diagnosis and managing CIN given its protean manifestations in patients who are already at risk for encephalopathy due to other causes.

Funding None.

Declarations

Conflict of interest Drs. Freund and Husari have no conflicts to report. Dr. Kaplan receives honoraria from Demos and Wiley textbooks, has served as expert witness on quantitative EEG and issues of coma and EEG, and is on the DSMB for EpiWatch.

Ethical approval Not applicable.

Informed consent Not applicable.

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