#1638

Encephalopathy in the Setting of Cefepime Use – Incidence and the Complexities in Assessing Etiology

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Abstract

Background: Cefepime-induced encephalopathy (CIE), while reported in case reports, is considered an uncommon toxicity. Patients admitted to the hospital requiring broad spectrum antibiotics with cefepime who develop encephalopathy often have multiple other etiologies for this finding. However, prescribers often look to modify antibiotic therapy for patients that develop encephalopathy while on cefepime given the reported association with this toxicity, which may result in selection of more toxic or less efficacious antibiotics.

Methods: We evaluated cefepime orders modified based on concern for CIE reported to our antimicrobial stewardship service among adult inpatients between 1/1/2016 to 5/10/2017 to identify the incidence of suspected CIE. We also assessed the likelihood of the encephalopathy being related to cefepime (based on number of additional potential etiologies and symptom resolution following cefepime discontinuation). Data on type of infection, location at time of antibiotic modification, and alternative antibiotics initiated was also collected.

Results: Eighteen patients developed suspected CIE for which the antibiotic was modified to an alternative anti-Pseudomonal agent. During the assessment period, there were 4,446 encounters where patients received cefepime. The observed suspected CIE incidence was 0.4%. The average cefepime duration prior to discontinuation was 7.3 days. The average number of additional potential etiologies was 4.8. In 3 patients, after discontinuation of cefepime as the only modification, symptoms of encephalopathy improved or resolved within 3-4 days. An EEG was performed on 17 patients, 9 EEGs showed triphasic wave forms consistent with encephalopathy. The baseline characteristics and modifications in antimicrobial therapy are summarized in Table 1.

Conclusion: The incidence of suspected CIE in our analysis was 0.4%. After removing those patients where symptoms did not resolve after discontinuing cefepime in the absence of other interventions, the observed incidence was more likely 0.07%. Given that the patients reviewed had an average of 4-5 other likely etiologies for their encephalopathy makes it difficult to truly identify the cause of encephalopathy in these cases.

Background

- Encephalopathy is a rarely reported toxicity associated with the use of cefepime, most available data consists of case reports and case series
- The primary risk factor identified in available literature for Cefepime induced encephalopathy (CIE) is the presence of renal impairment
- CIE typically manifests as altered mental status, confusion, cognitive disturbances and seizures
- The true incidence of CIE is not clear as often the occurrence of symptoms may not always be recognized as an artifact of cefepime use (may be a result of a multitude of other etiologies).
- We sought to assess the incidence of CIE, identify the baseline characteristics and number of additional potential etiologies among those with suspected CIE, and review if any unfavorable changes in antibiotic therapy resulted when CIE was suspected

Methods

Study Design
- Retrospective, observational, single-center study
- Analysis period: 1/1/2016 - 5/10/2017

Study Population
- Adult patients ≥ 18 years that received cefepime and changed to an alternative anti-Pseudomonal antibiotic as a result of concern for CIE

Primary Endpoint
- Identify the incidence of CIE

Secondary Endpoints
- Assess likelihood of CIE in each suspected case (based number of additional etiologies for encephalopathy and resolution of symptoms after cefepime discontinuation)
- Characterize patients with suspected CIE
- Identify adverse consequences of altering antibiotic therapy for suspected CIE

Statistical Analysis
- Descriptive statistics for summarizing incidence, patient characteristics, and other potential etiologies

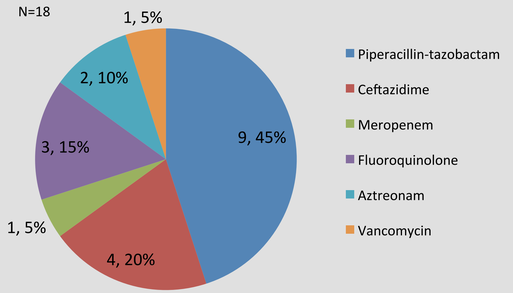
Results

- Out of 4,446 encounters during the time frame included in which patients received cefepime:
  - The observed incidence of **suspected CIE**: **0.4% (18/4446)**
  - The observed incidence of **likely CIE** (*based on resolution of symptoms of CIE following cefepime discontinuation):* **0.07% (3/4446)**

Table 1: Patient Characteristics (N=18)

Baseline Characteristics	
Gender, Male, n (%)	6 (33)
Age (median)	63.5
ICU Admission	9 (50)
General Medicine	5 (27)
Hematology/Oncology	3 (17)
Cefepime Indications	
Sepsis	3 (17)
Pneumonia	6 (33)
Febrile Neutropenia	3 (17)
SSTI/wound infection	4 (22)
Intra-abdominal infection	1 (5.5)
Fever, leukocytosis, unknown source	1 (5.5)

Figure 1: Alternative Anti-Pseudomonal Antibiotics (Switch from Cefepime)*



*Some patients changed from cefepime to 2 different antibiotics (e.g. cefepime changed to ceftazidime and vancomycin)

Table 2: Modifications in Antibiotic Therapy

Changed to Inappropriate Therapy *(Piperacillin-tazobactam, patient grew Enterobacter)*	1
Required Combination Antibiotic Regimen *(e.g. ceftazidime + vancomycin for febrile neutropenia)*	3
More Toxic Antibiotic *(e.g. Ciprofloxacin in patient with prolonged QTc, addition of vancomycin)*	5*

*2 patients changed to fluoroquinolone alone, the remaining 3 patients received vancomycin or a fluoroquinolone in addition to alternative beta-lactam

Table 3: Suspected CIE, Reaction Characteristics

Time to onset (Days), mean	7.3
Time to resolution after DC (days), mean (range)	3.3 (1-5)
Additional Possible Etiologies, mean (range)	4.8 (3-9)
Number of Patients with Confirmed Alternative Etiologies *(based on continued symptoms despite discontinuation of cefepime or identification of specific etiology, e.g. hemorrhage, new brain lesions, stroke)*	7
Number of Patients with Unconfirmed Etiology *(Unclear if symptoms improved as result of discontinuing cefepime or other interventions e.g. dialysis if also hyperammonemic, high drug levels of agents known to cause similar symptoms, multiple additional medications associated with similar symptoms)*	8
Number of Patients with Likely CIE *(based on resolution of symptoms with cefepime discontinuation as the primary intervention)*	3

Table 4: Patient Cases with Discontinuation of Cefepime as Primary Intervention, with Resolution of Symptoms (n=3)

Patient Age, Gender	Cefepime Dose/ indication	Renal function	Possible Additional Etiologies (total #)	EEG Finding*	Duration cefepime (mean)	Time to resolution (mean)
80, F	1G Q8H Sepsis, PNA	CrCl:35	Sepsis, hypotension, chronic small vessel ischemic disease (3)	Triphasic waveforms	4 days	3 days
78, F	1G Q12H Sepsis, UTI	CKD CrCl: 17	Sepsis, uremic, baseline history of epileptic activity (on levetiracetam), dementia at baseline (4)	Triphasic waveforms	5 days	4 days
64, F	1G Q8H PNA	CrCl:59	Microvascular ischemic disease, CVA, seizures, metabolic, infection, toxins (6)	Triphasic waveforms	4 days	4 days

PNA: Pneumonia, CVA: Cerebrovascular accident, iHD: intermittent hemodialysis, CrCl: creatinine clearance
*Electroencephalogram (EEG) findings commonly reported in case reports of CIE include: triphasic waveforms, diffuse slowing, and multifocal sharp waves

Conclusion

- After removing patients where symptoms resolved as result of other modifications in therapy or cases where symptoms persisted despite stopping cefepime, the overall incidence of likely CIE in our analysis was 0.07%
- Six patients (33.3%) received alternative antibiotics that were more toxic or inappropriate based on culture data
- The patients with likely CIE, were all >=64 years old (mean : 74 years old), and had an estimated CrCl of <=60 ml/min (mean :37 ml/min).
- Clinicians should be mindful of the low incidence of CIE and consider other potential etiologies when assessing changes in mental status or other signs/ symptoms of encephalopathy
- Making empiric changes in antibiotic therapy as a result of concern for CIE can result in the implementation of suboptimal or more toxic antibiotic regimens

References

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Disclosure

The authors of this presentation have no financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation