Beta-Lactam Neurotoxicity (Including Cefepime)

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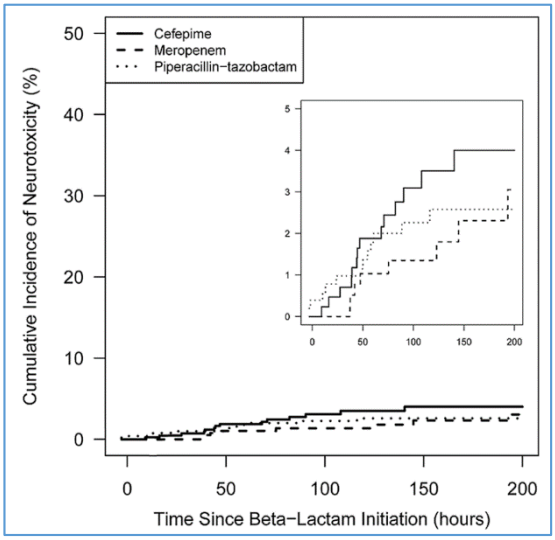
What is beta-lactam neurotoxicity and cefepime-induced neurotoxicity (CIN)?[1-15]

- **Definition:** Neurologic changes or symptoms associated with anti-pseudomonal beta-lactams (cefepime, meropenem, piperacillin-tazobactam)
  - Literature primarily implicates cefepime, however recent literature indicates this can happen with all anti-pseudomonal beta-lactams
- **Proposed mechanism:** Beta-lactams can cross the blood-brain-barrier (BBB) and exhibit concentration-dependent GABA antagonism/prevent release of GABA
- **Onset:** >2 days of therapy
- **Overall Incidence: <u>2-3%</u>**

Risk Factors[11, 12]
- Elderly
- Renal dysfunction
- Excessive dosing/high dosing – especially in conjunction with renal dysfunction
- Doses >4 grams per day
- Elevated serum cefepime concentrations (>20 mg/L)
- Pre-existing brain injury
- BMI >30 kg/m^2

Symptoms: Most symptoms come from retrospective studies using cefepime:[11,12]
- <u>No consistent definition</u> among different studies (ranges from decreased level of consciousness to non-convulsive status epilepticus or seizures)

Data Regarding Beta-Lactam Associated Neurotoxicity (CIN):
- **New Studies:**
  - **Haddad et al:[15]** found overall incidence of beta-lactam neurotoxicity to be **<u>2-3%</u>** (figure to the right)
    - Excluded other causes of neurologic changes (ex: alcohol, benzodiazepine, delirium, paralytics, brain injury, stroke, drug overdose, etc.)
    - Definition: positive cases identified by the Naranjo Scale by 2 out of 3 manual chart reviewers
    - **Conclusion:** beta-lactam neurotoxicity is rare
  - **Beumier et al:[14]**
    - Found neurologic worsening (NW) associated with higher beta-lactam concentrations:
      - NW: associated with increasing C_{min}/MIC ratio (p = 0.008)
        - When broken down by specific medications, only piperacillin-tazobactam and meropenem remained statistically significant (p = 0.05 and 0.01 respectively) whereas cefepime/ceftazadime did not demonstrate statistical significance with increasing concentrations



- **Old Studies:**
  - Previous attention on cefepime in the literature, with 1-15% neurotoxicity rate reported, but data are heterogenous and have several limitations. [2-12]
    - Mostly case reports, single-center case series, retrospective studies
    - Lacked comparator groups
    - Did not control for confounders
    - Studies used different definitions of CIN

Assessment: screening checklist[2-13]

Does the Patient Have the Following? – if "yes" to any consider other causes

- ☐ Alcohol dependence or undergoing alcohol withdrawal
- ☐ Dementia
- ☐ Epilepsy
- ☐ Drug Overdose
- ☐ Stroke, traumatic brain injury, brain hemorrhage
- ☐ Glascow coma score of <8
- ☐ Delirium
- ☐ Receiving concomitant paralytic agents (cisatracurium)
- ☐ Richmond Agitation Scale Score <4 within 48 hours
- ☐ Use of benzodiazepines in previous 48 hours (lorazepam)

When was the beta-lactam started before onset? – if <2 days consider other causes

- ☐ ≥2 days

Is the beta-lactam dosed appropriately for renal function? – if "yes" consider other causes

- ☐ Cefepime
- ☐ Piperacillin-tazobactam
- ☐ Meropenem

Assess for Risk Factors: if no risk factors consider other causes

- ☐ Does the patient have any risk factors above?

If other causes excluded and patient needs pseudomonal coverage:

- ☐ Try switching to a different antipseudomonal beta-lactam
- ☐ Consider non beta-lactam
- ☐ Trial off of antibiotic to determine if symptoms resolve

If other causes excluded and patient does not need pseudomonal coverage:

- ☐ Consider de-escalation to a non-pseudomonal beta-lactam or non beta-lactam (guided by site of infection, cultures and sensitivity)

Conclusions:

1. Beta-lactam neurotoxicity is **rare (2-3% incidence)** and is a diagnosis of exclusion
2. Ensure appropriate renal dose adjustment (cefepime, pip-tazo, meropenem)
3. Evaluate opportunities for de-escalation to non-pseudomonal beta-lactams

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