Cefepime vs Piperacillin-Tazobactam for Acute Infection?

Key Article

- *Qian ET, Casey JD, Wright A, et al. Cefepime vs Piperacillin-Tazobactam in adults hospitalized with acute infection. The ACORN Randomized Clinical Trial. JAMA. 2023; 330:1557-67.*

Background

- Timely and appropriate administration of empiric antibiotics for acutely ill adult patients presenting with suspected infection is critical.
- For patients at risk of resistant gram-negative infections, current guidelines recommend an antipseudomonal antibiotic, such as cefepime or piperacillin-tazobactam.
- In recent years, observational studies have reported an association with cefepime and neurotoxicity, whereas piperacillin-tazobactam has been associated with AKI especially when given with vancomycin.
    - Cefepime crosses the blood-brain barrier, exhibits concentration-dependent inhibition of GABA receptors, and is associated with neurotoxicity – coma, delirium, encephalopathy, and seizures. Neurotoxicity reported to be more common in patients with impaired kidney function and conditions that disrupt the BBB.
    - Piperacillin-tazobactam decreases secretion of creatinine into the urine and increases creatinine in the blood by inhibiting an organic anion transporter on kidney tubular cells.
- At present, no randomized trial has compared cefepime with piperacillin-tazobactam.

Objective

- To compare the safety of cefepime vs piperacillin-tazobactam in adults presenting to the hospital with suspected infection.

Methods

- Pragmatic, open-label, parallel-group, randomized comparative trial.
- ED and MICU of Vanderbilt University Medical Center
- Patients
    - Included:
        - Adults $\geq$ 18 years
        - In the ED or MICU
        - Had a clinician-initiated order for cefepime or piperacillin-tazobactam within 12 hours of presentation to the hospital.
    - Excluded
        - Age < 18 years
        - Allergy to cephalosporins or PCN
        - Received more that 1 dose of an antipseudomonal ABX or PCN within the previous 7 days.
        - Incarcerated

        - Treating clinician determined that 1 or the 2 drugs represented a better treatment option.
- Trial procedures
    - Randomized in 1:1 ratio to receive cefepime or piperacillin-tazobactam.
        - Cefepime Group – 2 g IV push over 5 minutes every 8 hours
        - Piperacillin-tazobactam Group – 3.375 g bolus over 30 minutes for the initial administration followed by an extended infusion of 3.375 g every 8 hours.
    - Treating clinician determined the duration of ABX and whether to administer additional antibiotics, such as vancomycin.
    - Both the ED and MICU were staffed by dedicated clinical pharmacists
- Primary outcome
    - Highest stage of AKI or death by day 14
    - Used a 5-point ordinal scale and the stage of AKI defined using the KDIGO criteria.
- Secondary outcomes
    - Proportion of patients who experienced a major adverse kidney event at day 14 (composite of death, new RRT, or persistent renal dysfunction)
    - Number of days alive and free of delirium and coma within 14 days (assessed using the CAM-ICU or RASS score)

Results

- A total of 2,511 patients were included in the primary analysis.
    - Median age was 58 years.
    - 95% enrolled in the ED.
    - Median time between presentation and enrollment was 1.2 hours.
    - 54% had sepsis at the time of enrollment, with intra-abdominal and pulmonary the most common sources.
- Randomization
    - Cefepime Group: 1,214 patients (48.3%)
    - piperacillin-tazobactam Group: 1,297 (51.7%)
- Antibiotic Therapy
    - Median duration of receiving assigned ABX: 3 days
    - Crossover
        - Cefepime Group: 19% received at least 1 dose of piperacillin-tazobactam.
        - Piperacillin-Tazobactam Group: 17% received at least 1 dose of cefepime.
    - Vancomycin
        - Cefepime Group: 83% received at least 1 dose of vancomycin.
        - Piperacillin-tazobactam: 81% received at least 1 dose of vancomycin.
        - Median duration of vancomycin: 2 days
- Primary Outcome – Highest stage of AKI or death by day 14
        - No statistical difference between the groups
        - Cefepime Group: 75% did not die or experience AKI of any stage.
        - Piperacillin Group: 73% did not die or experience AKI of any stage.
- Safety Outcomes
    - Major Adverse Kidney Event
        - Cefepime Group: 10.2%
        - Piperacillin-Tazobactam: 8.8%
        - No statistically significant difference

- Coma/Delirium by Day 14
  - Cefepime Group: 20.8%
  - Piperacillin Group: 17.3%
  - Met statistical significance – patients in the cefepime group had fewer days alive and free of delirium and coma.

Limitations Identified by Authors

- Single center – Vanderbilt University – generalizability?
- Clinicians unblinded to group assignment
- Almost 20% of patients in each group received the unassigned ABX within the first 14 days.
- The median duration of ABX was 3 days.
- Assessment of neurotoxicity only focused on delirium and coma – did not assess agitation, myoclonus, and seizures.
- Cefepime administered as IVP compared to piperacillin-tazobactam which was administered as extended infusion.

Take Home Points

- Among hospitalized adults with suspected infection, piperacillin-tazobactam did not increase the incidence of AKI or death, even when given with vancomycin.
- Among hospitalized adults with suspected infection, cefepime was associated with a greater incidence of neurotoxicity.