Different CRRT Effluent Rates likely Impact Optimal Cefepime Extended-Infusion Doses

Varying CRRT Effluent Rates Alter the Probability of Target Attainment of Cefepime Extended-Infusion Dosing

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INTRODUCTION

- Cefepime, an antipseudomonal cephalosporine, is commonly prescribed to treat critically ill patients on continuous renal replacement therapy (CRRT) experiencing sepsis and acute kidney injury.
- Cefepime's maximal efficacy is predicted by the time of the free serum concentration above 4x the minimum inhibitory concentration (fT >4x MIC) and Extended infusion strategy can improve the attainment of this efficacy target.[1]
- Currently, a lack of data exists to guide clinicians regarding optimal cefepime extended infusion dosing regimens in patients receiving CRRT at different effluent rates.

OBJECTIVES

- The purpose of this study was to predict optimal extended infusion cefepime doses attaining the efficacy target in this patient population using Monte Carlo Simulations (MCS) and to evaluate the effect of different CRRT effluent rates on the optimal cefepime extended dosing regimens.

METHODS

Pharmacokinetic (PK) Modeling

- Pertinent demographics and PK data found in the literature[2-10] were was incorporated to develop a 1 compartment, first-order pharmacokinetic (PK) model to evaluate the effect of continuous veno-venous hemofiltration (CVVH) with 3 different effluent rates (20, 30, & 45 mL/kg/h) on the plasma cefepime concentration for the first 48 hours.[11]

Modeled Demographic &Pharmacokinetic Parameters, mean ± SD [Range]	
Weight (kg)	0.86 ± 29.2 [≥40]
Volume of Distribution (L/kg)	0.48 ± 0.24 [0.16-1.11]
Non-renal Clearance (mL/min)	24.33 ± 11.25 [13-24]
Free Fraction	0.79 ± 0.09 [0-1]

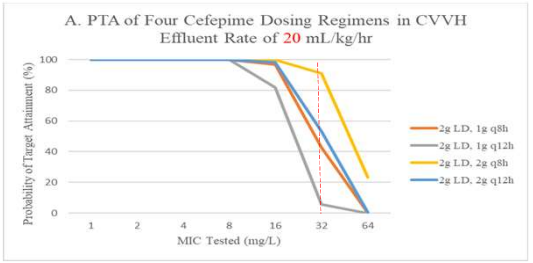
Monte Carlo Simulation (MCS)

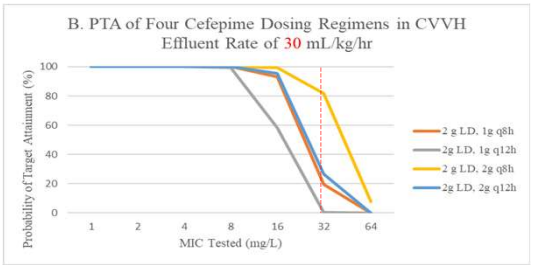
- Four conventional cefepime doses simulated were:
  2 g loading dose (LD) infused over 30 min, followed by
  1) 1 g q8h infused over 4 hours or
  2) 1 g q12 h infused over 4 hours or
  3) 2 g q8h infused over 4 hours or
  4) 2 g q12 h infused over 4 hours
- Plasma drug concentration-time profiles were generated by the MCS for 5,000 virtual subjects in 0.1-hour intervals for each cefepime dosing regimen.

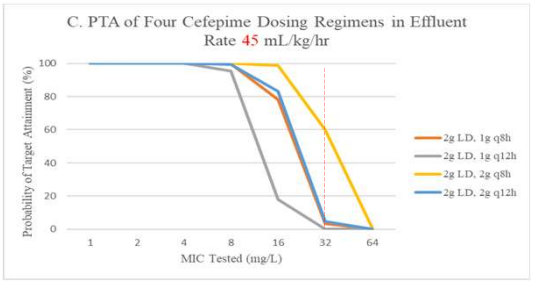
Pharmacodynamic (PD) Target:

- The MIC of *Pseudomonas aeruginosa* is 8 mg/L.[12]
- The PD target of cefepime was attainment of fT >4x MIC (=32 mg/L) for ≥60% of the first 48 hours of therapy.
- Cefepime toxicity risk was surveyed using the reported toxicity threshold of >70 mg/L at the end of 48 hours of therapy. [13]
- **Optimal Dose:** Doses that reached Probability of Target Attainment ≥ 90% with the lowest toxicity risk.

RESULTS







DISCUSSION

- MCS predicted that cefepime 2 g LD followed by 2 g every 8 hours would be the optimal extended infusion dosing regimen in patients receiving CVVH at effluent rates of 20 mL/kg/hr. The risk of drug toxicity was negligible in these patients.
- However, higher than usual cefepime doses would be needed to reach ≥90% PTA if the CVVH effluent rates is greater than >20 mL/kg/hr.
- Different CRRT effluent rates appear to influence on the optimal extended infusion cefepime doses.
- The findings of this simulation study would support a clinician's decision to optimize extended infusion cefepime doses in patients with CVVH. Further clinical validation would be warranted.

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DISCLOSURES

Authors declare no conflict of interest.

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