Monte Carlo Simulations (MCS) of Various Cefepime Dosing Strategies in Children Receiving CRRT Support Continuous Infusions for Pharmacodynamic Target Attainment

H. Rhodes Hambrick, MD[1,2], Nieko Punt[3,4] Tomoyuki Mizuno, PhD [2,5], Stuart L. Goldstein, MD[1,5,6], Sonya Tang Girdwood, MD PhD[2,5,7]

[1]Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center (CCHMC), [2]Division of Translational and Clinical Pharmacology, CCHMC, [3]Medimatics, Maastricht, Netherlands, [4]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, [5]Department of Pediatrics, University of Cincinnati College of Medicine, [6]Center for Acute Care Nephrology, CCHMC [7]Division of Hospital Medicine, CCHMC

Introduction

- Sepsis is a leading cause of AKI requiring CRRT and antibiotics are cornerstone of tx
- CRRT can alter drug pharmacokinetics (PK)
- Cefepime is commonly used for sepsis and is cleared by CRRT, but data are scarce regarding cefepime PK and pharmacodynamic (PD) target attainment in children on CRRT
- Reported extracorporeal clearance (CL_{EC}) of cefepime in existing case reports (n=4 to 7) in children varies widely, from 30-70% of total cefepime CL (CL_{tot})

Methods and Materials

- Adapted a pediatric cefepime PK model[1] to have a CRRT module based on an existing CRRT model[2], including blood flow, filter size, and dialysis/replacement fluid flow rates/total effluent flow (Q_{ef}) (**Fig 1**)
- Tested 6 cefepime dosing strategies in 3 age groups w/ corresponding filter sizes (Baxter ST60, ST100, or ST150) with varying parameters:
  - 0 to 30% fluid accumulation
  - Q_{ef} 2500 vs 8000 mL/hr/1.73 m^2
- Performed 1000-fold Monte Carlo Simulations (MCS) to assess probability of target attainment (PTA) of free concentrations exceeding 1x and 4x minimum inhibitory concentration for 100% of time (100% *f*T>1x/4x MIC)
  - Used an MIC of 8 mg/L for *Pseudomonas aeruginosa*
- Assumed minimal residual kidney function (eGFR 5 mL/min/1.73 m^2)

Results

- MCS results are shown in **Figure 2a-c**.
- Continuous infusions (CI) of 100 mg/kg (max 4g) or 150 mg/kg (max 6g) achieved >90% PTA for 100%*f*T>1x MIC (left panels) in all cases, regardless of CRRT Q_{ef}.
- 4h infusions of 50 mg/kg (max 2g) every 8 hours (q8h) achieved >90% PTA for 100%*f*T>1x MIC for standard dose dialysis. 30m infusions of 50 mg/kg q8h (max 2g) achieved this same target for standard-dose dialysis in patients ≥5 years of age and 2 to <5 y.o. with ≥10% fluid accumulation.
- For, 100%*f*T>4x MIC (right panels), >90% PTA was only achieved by 150 mg/kg (max 6g) CI for standard-dose dialysis.
- Decreased PTA was seen with less frequent dosing, shorter infusions, higher-dose CRRT, and lesser degrees of fluid accumulation.
- The ratio of CL_{EC}/CL_{tot} varied from 42-66%, with higher CL_{EC} correlating with higher BSA-indexed Q_{ef} (r^2 = 0.99)

Figure 1: CRRT pharmacokinetic model used for simulations

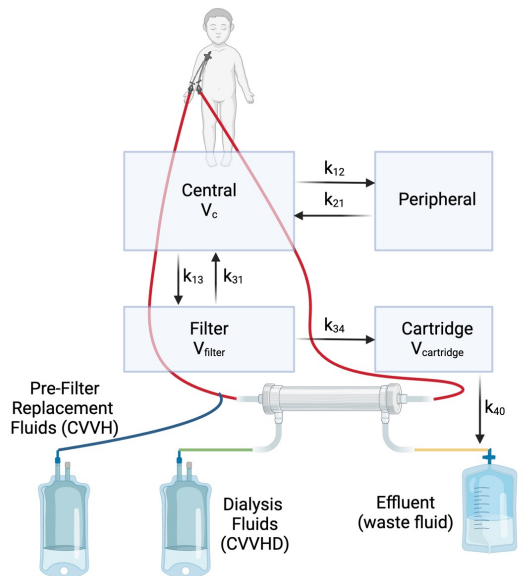


Figure 2a: 2 to <5 y.o.

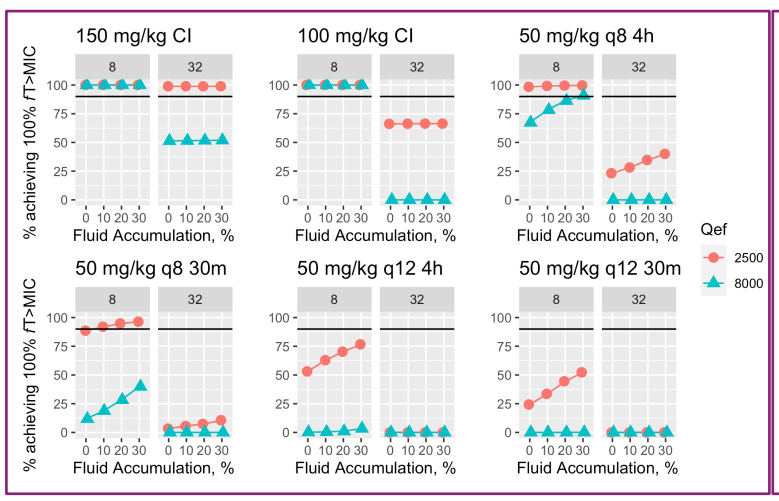


Figure 2b: 5 to <12 y.o.

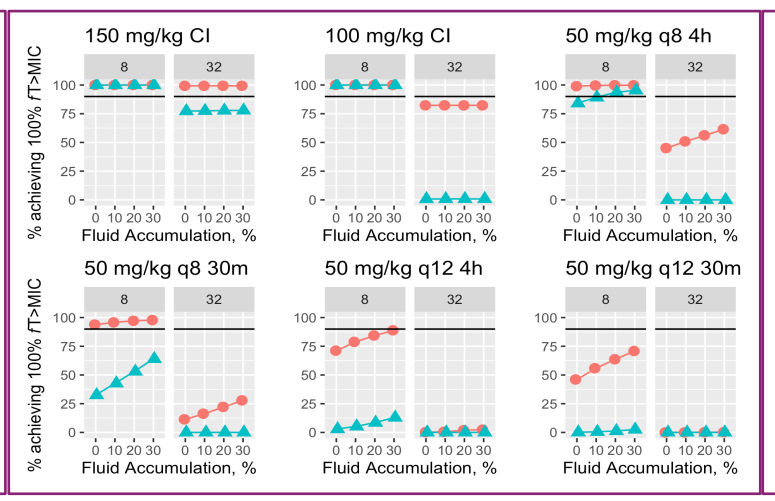
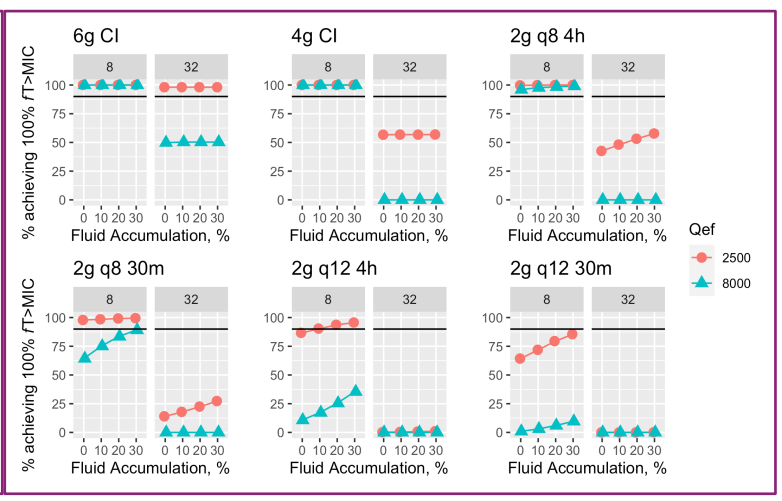


Figure 2c: 12 to <25 y.o.



Discussion/Conclusions

- Continuous infusions of cefepime may be warranted in children receiving CRRT to achieve stringent PD targets
- A prospective study to validate these simulations results in real-world patients is ongoing

References

1. Shoji K et al. *Antimicrob Agents Chemother* 2016;**4**:2150-6.
2. Nehus EJ et al. *J Clin Pharmacol* 2014;**12**:1421-8.

Acknowledgments

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