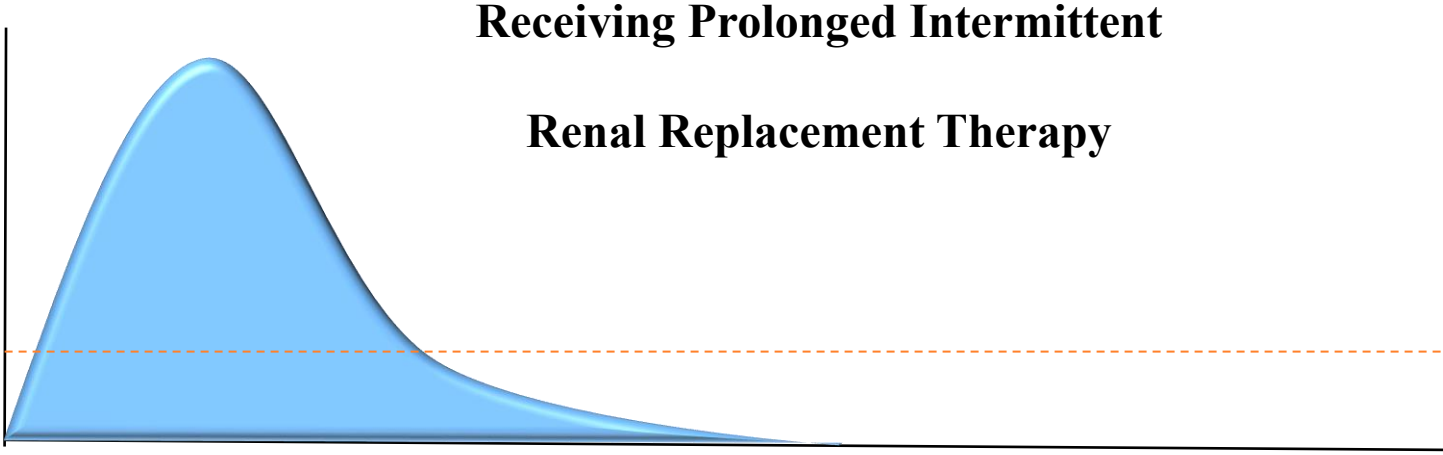
Antibiotic Dosing in Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapy



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PUBLICATIONS

Gharibian KN, Mueller BA. Fluconazole Dosing Predictions in Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapy: A Monte Carlo Simulation Approach. *Clin Neph* 2016 Jul;86(7):43-50.

Lewis SJ, Kays MB, Mueller BA. Use of Monte Carlo Simulations to Determine Optimal Carbapenem Dosing in Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapy. *J Clin Pharmacol* 2016 Feb 26. doi: 10.1002/jcph.727.

Lewis SJ, Chaijamorn W, Shaw A, Mueller BA. *In silico* Trials Using Monte Carlo Simulation to Evaluate Ciprofloxacin and Levofloxacin Dosing in Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapy. *Renal Replacement Therapy 2016* 2:45.

POSTER PRESENTATION (PENDING PUBLICATION)

Lewis SJ, Gharibian KG, Tolwani AJ, Fissell WH, Mueller BA. Evaluation of Piperacillin/Tazobactam Regimens in Patients with SHIFT Renal Replacement Therapy. Oral Poster Presentation SA-PO532, 2015 ASN.

BACKGROUND

Sepsis is a primary cause of mortality in critically ill patients requiring renal replacement therapy (RRT)[1], resulting in a great healthcare burden and challenge for prescribing clinicians. Despite the availability of antibiotics to treat infection, there is a lack of pharmacokinetic (PK) data to determine optimal dosing levels, leading to widely inconsistent dosing prescriptions and raising serious concerns that pharmacodynamics targets are not routinely being met and are contributing to the high rates of mortality observed in this patient population.[2,3]

With the increasing prescription of hybrid renal replacement therapies, the challenge is compounded as less than 1% of the drugs used in critically ill patients have PK data for this modality. Prolonged intermittent renal replacement therapy (PIRRT) is a 6 – 12 hour hybrid renal replacement therapy that may be used as a viable alternative to conventional intermittent hemodialysis (IHD) or continuous renal replacement (CRRT). PIRRT provides the benefits of better patient mobility compared to CRRT, and gentler fluid removal over a slightly longer treatment period than with IHD. With these unique benefits and similar patient outcomes compared to conventional RRT, PIRRT is becoming more widely adopted by clinicians as a viable treatment option for patients with AKI.[4,5,6,7,8] Variations in prescription, therapy time and use of equipment have resulted in the use of different terms for such a hybrid modality including PIRRT, SLEDD, Accelerated Veno-venous Hemofiltration (AVVH), as well as SHIFT, since the therapy can be delivered within a typical nursing shift.

The cost of studying each antibiotic for the various forms of RRT would be cost-prohibitive, however, the use of an *in silico* model using Monte Carlo simulations can be used to predict optimal drug dosing regimens.

METHODS

Using techniques borrowed from disciplines including infectious disease, pharmacometrics, pharmacokinetics, and LEAN business theory, Mueller, et al, developed a computerized model that combines antibiotic *in silico* modelling with pharmacokinetic data from critically ill patients, with an understanding of drug clearance by hybrid RRT.[9] This pharmacometric probability model accounts for known patient, RRT, pharmacokinetic, pharmacodynamic variability and predicts antibiotic dosing regimens that are likely to achieve serum concentration targets in critically ill patients with AKI receiving PIRRT. Known pharmacokinetic variances derived from published literature are applied to virtual “patients” with variability in body size, protein binding rates and hepatic function. Patients can be “dosed” with antibiotics at different times relative to their RRT using Monte Carlo simulation. These *in silico* trials allow “dosing” thousands of different virtual patients to determine the effects of antibiotic dose and SHIFT on attained antibiotic serum concentrations. *In silico* models using Monte Carlo simulation have been used extensively for

decades, with clinical validation demonstrating that this approach can be successful in guiding dosing levels when clinical trials are impractical.[10,11,12,13] To show that this model can be used to predict pharmacodynamic target attainment in patients receiving a PIRRT, Meropenem disposition in patients receiving a form of hybrid dialysis called Extended Daily Dialysis (EDD) was modeled and published by Kielstein et al.[14]

This *in silico* model was used to study ten of the most commonly used antibiotics in the ICU (Table 1), with a probability of target attainment (PTA) of 90% at minimum inhibitory concentrations in critically ill patients receiving 8 and 10 hour RRTs (Table 2). This study format allowed the inclusion of thousands of virtual subjects per drug tested (n=5,000/tested dose). The incorporation of previously published patient demographics and pharmacokinetic parameters allow for the predictability of safety and efficacy.[9,15]

ANTIBIOTICS STUDIED

Table 1

CLASSIFICATION	ANTIBIOTIC AGENTS	APPLICATION IN ICU
Carbapenems	Ertapenem, Meropenem, Imipenem	Gram negative infections
Cephalosporin/penicillin	Cefepime, Ceftazidime, Piperacillin/Tazobactam	Gram negative infections
Fluoroquinolone	Ciprofloxacin, Levofloxacin	Gram negative pathogens
Glycopeptide	Vancomycin	Gram positive infections (staph infections)
Triazole Antifungal	Fluconazole	Antifungal antibiotic

OPERATIONAL PARAMETERS

Table 2

Operational Parameters	
Weight (kg) based on published data[9]	86.6±29.2 [≥40]
RRT operating parameters:	
Modality	Hemodialysis or Pre-dilution Hemofiltration
Frequency	Daily
Blood Flow Rate	300 mL/min
Dialysate/Ultrafiltration flow rate & duration	4 L/h for 10 h or 5L/h for 8 h

RESULTS

Table 3

ANTIBIOTIC	DOSING RECOMMENDATION
Meropenem	1g q12h or 1g pre & post SHIFT treatment
Imipenem	750mg q6h or 1g q8h
Ertapenem	500mg upon SHIFT initiation, then 500mg post-SHIFT treatment
Piperacillin /Tazobactam	4.5g q6h
Cefepime	2g LD, then 4g 24h-continuous infusion or 3g LD, then 1g q6h
Ceftazidime	2g q12h
Levofloxacin	G- No non-toxic dose can reach the target G+ 750 mg LD, 500mg post-SHIFT treatment
Ciprofloxacin	No non-toxic dose can hit target
Vancomycin	15mg/kg now and post-SHIFT treatment
Fluconazole	800mg LD, 400mg pre & post SHIFT treatment

STUDY LIMITATIONS

Patients were assumed to be adult ($\geq$40kg) with negligible renal drug clearance, and were characterized with literature-based demographic and PK parameters. This was a one-compartment model. PK parameters used in the model included data from non-anuric patients, as well. The model incorporated the use of PIRRT on a daily basis, therefore, recommendations should be applied appropriately to those who match these demographic and PK parameters and frequency of therapy.

CONCLUSION

These *in silico* simulations provide rational dosing guidelines for clinicians treating critically ill patients receiving an 8 or 10 hour RRT and should be used until clinical validation studies can be completed.

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IMPORTANT INFORMATION

Renal replacement therapy, as with any medical therapy is not without risks. The decision of which therapy to use should be made by the physician, based on previous experience and on the individual facts and circumstances of the patient.