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WHAT'S NEW IN INTENSIVE CARE

What's new in pharmacokinetics of antimicrobials in AKI and RRT?

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Acute kidney injury (AKI) remains a very common occurrence in critically ill patients and is associated with decreased survival in severe sepsis [1]. Effective treatment for these patients is mostly through treatment of the underlying pathology as well as supportive care with renal replacement therapy (RRT). Optimised pharmacotherapy is of heightened importance to ensure maximal outcomes for critically ill patients with AKI receiving RRT, although the pharmacokinetics of many drugs can change dramatically in these patients, making effective dosing a challenge.

The purpose of this paper is to describe the new developments in antibiotic dosing and pharmacokinetics in critically ill patients with AKI and receiving RRT.

The overwhelming body of recent literature aims to understand how to better dose these compounds in critically ill patients receiving different forms of RRT, with far more data being generated for continuous than for intermittent RRT. Little data is available in AKI without RRT. Very few data on other classes of drugs are available which is largely due to the fact that many have negligible RRT clearance because of high protein binding, hepatic clearance or large volumes of distribution (e.g. most anticonvulsants), have dosing that is titrated to effect (e.g. analgesics and sedatives) or have readily available therapeutic drug monitoring (TDM).

Recent pharmacokinetic studies of antibiotics have moved away from a drug-based dosing approach, where each drug has a given dose regardless of type of RRT, to a strategy where the specific drug dose accounts for the modality of RRT (e.g. intermittent, prolonged or continuous convective and/or diffusive RRT) and the associated settings (e.g. blood or ultrafiltration flow rate, filter material and surface area).

Most of the studies continue to evaluate only pharmacokinetic endpoints and include small cohorts which limits the generalizability of findings. On the other hand, some comparative studies have been useful to better elucidate the effect of different approaches to RRT, including different modalities (i.e. intermittent and prolonged intermittent RRT and CRRT). It is hoped that the forthcoming SaMpling Antibiotics in Renal Replacement Therapy (SMARRT) study (ACTRN12613000241730), endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG), will address many of these issues. Further to this, use of ex vivo models of RRT are providing suitable doses for drugs to be subsequently tested in clinical pharmacokinetic studies [2]. Such models are very useful as the interaction between changing RRT modalities and settings on drug clearance, as well as potentially significant drug adsorption to the RRT membrane, can be more accurately calculated without the complicating effects of biology.

Important knowledge has been generated recently that has aimed to quantify the effect of the dose and type of RRT used. Using a meta-review methodology of published studies, Jamal et al. highlighted the importance of CRRT dose where they found that extracorporeal CRRT clearance was correlated with effluent flow rate for meropenem, piperacillin and vancomycin [3]. Another important report came from the pharmacokinetic substudy [4], within the RENAL study [5], which was a multinational randomised controlled trial (RCT) that compared the effect of two different continuous venovenous haemodiafiltration (CVVHDF) doses, 25 versus 40 mL/kg/h, on patient survival. After controlling for filter age and downtime, the authors observed that meropenem,

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piperacillin, vancomycin and ciprofloxacin clearance was always numerically higher with the 40 mL/kg/h cohort, although the difference was only significant for vancomycin (22% higher clearance in the 40 mL/kg/h group, $p < 0.01$). However, the dramatic variability in drug concentrations led the authors to conclude that singular dose recommendations were not possible and that TDM was the only way to ensure consistently effective doses. Indeed TDM is likely to be more valuable in RRT than in other scenarios because of dramatic pharmacokinetic variability, even whilst acknowledging the challenges of establishing TDM for some drugs like colistin.

It is important to note that suggestions that dosing recommendations for singular creatinine clearance can be assumed to be acceptable for RRT dosing (e.g. 30 mL/min) are also unfounded as some drugs such as fluconazole and colistin can have much higher clearances during RRT because of the absence of tubular resorption which would maintain higher concentrations in patients with residual renal function [6, 7].

A series of studies from Roger et al. recently studied the effect of the type of RRT, as pharmacokinetic substudies of a clinical trial that compared the same dose of RRT, administered as either continuous venovenous haemofiltration (CVVHF) or CVVHDF. The drugs of interest included amikacin [8], ciprofloxacin [9] and linezolid [10]. Surprisingly there was no consistent effect of the type of CRRT. For the renally cleared amikacin and ciprofloxacin, CVVHF had a modestly higher mean drug clearance (5.2% and 12.8%, respectively) whereas CVVHDF resulted in a higher mean clearance for linezolid (20.5%). Recommended dosing regimens for amikacin and linezolid were 25 mg/kg 36–48-hourly and 600 mg 12-hourly, respectively. Each of these reports, like most RRT pharmacokinetic studies, observed high pharmacokinetic variability highlighting that comparison of mean parameter values or concentrations can be misleading. Therefore, understanding the distribution of these values is important to understand the range of dosing possibilities for any drug–RRT combination.

The effect of the residual renal function of the patient on meropenem dosing requirements was investigated by Ulldemolins et al.; the authors found that the volume of residual diuresis was important with urine outputs greater than 500 mL/day, requiring an additional dose per 24-h period or administration by an extended infusion [11].

Further exploration of the role of changing the method of infusion of beta-lactams was separately performed by Shotwell et al. [12] and Jamal et al. [13, 14]. Shotwell and colleagues analysed piperacillin concentrations in 68 CRRT patients. The authors found that only 45% of patients achieved their therapeutic target (mid-dosing interval concentration greater than 64 mg/L) with an 8 g/day dose whereas this increased to 95% with 12 g/day dosing. The importance of infusion duration of beta-lactams was emphasised by two RCTs from Jamal et al. of meropenem [13] and piperacillin [14]; the authors found that administration as a continuous infusion resulted in higher achievement of concentration targets than 30-min intermittent infusions did. Importantly though, prolonged infusions were observed only to be useful for less susceptible pathogens, particularly if high doses are used empirically (the investigators used 3 g/day meropenem and 16 g/day piperacillin).

Another important emerging use of RRT is as an adjunctive therapy with aggressive antimicrobial dosing in order to achieve pharmacodynamics targets. In a pilot study of 15 patients, Brasseur et al. described the treatment of multidrug-resistant (MDR) Gram-negative sepsis with high-dose aminoglycosides and high-flow (greater than 45 mL/kg/h) CVVHDF [15]. The use of high-flow CRRT allowed the combination of a bactericidal concentration (peak/MIC ratio greater than 8) followed by rapid drug removal resulting in a safe trough concentration, in turn allowing an earlier subsequent bactericidal dose.

In conclusion, the recent literature relating to pharmacokinetics in RRT has demonstrated high interpatient variability and that a more consistently accurate approach to dosing remains elusive. Clinicians should be aware of prescribed and delivered RRT doses as well as the patient's residual renal function in considering dosing requirements for patients. Finally, we note the emergence of various new compounds in late phase studies, or that have been recently licensed, and we strongly recommend that appropriate dosing regimens be defined for RRT.

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Compliance with ethical standards

Conflicts of interest
The authors have no known conflicts of interest relating to this work. J.A.R. declares unrelated consultancies for bioMerieux, MSD, Astellas and Infectopharm over the last 3 years. J.L. and J.Y.L. declare no potential conflicts of interest.

Ethical approval
This article does not contain any studies with human participants or animals performed by any of the authors.

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References

1. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294:813–818
2. Jamal JA, Udy AA, Wallis SC, Ranganathan D, McWhinney BC, Ungerer JP, Lipman J, Roberts JA (2015) Can we use an ex vivo continuous hemofiltration model to describe the adsorption and elimination of meropenem and piperacillin? Int J Artif Organs 38:419–424
3. Jamal JA, Udy AA, Lipman J, Roberts JA (2014) The impact of variation in renal replacement therapy settings on piperacillin, meropenem, and vancomycin drug clearance in the critically ill: an analysis of published literature and dosing regimens. Crit Care Med 42(7):1640–1650
4. Roberts DM, Liu X, Roberts JA, Nair P, Cole L, Roberts MS, Lipman J, Bellomo R, RENAL Replacement Therapy Study Investigators (2015) A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics. Crit Care 19:84
5. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S (2009) Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 361:1627–1638
6. Muhl E, Martens T, Iven H, Rob P, Bruch HP (2000) Influence of continuous veno-venous haemodiafiltration and continuous veno-venous haemofiltration on the pharmacokinetics of fluconazole. Eur J Clin Pharmacol 56:671–678
7. Karaiskos I, Friberg LE, Galani L, Ioannidis K, Katsouda E, Athanassa Z, Paskalis H, Giamarellou H (2016) Challenge for higher colistin dosage in critically ill patients receiving continuous venovenous haemodiafiltration. Int J Antimicrob Agents 48:337–341
8. Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Lefrant JY, Roberts JA (2016) Influence of renal replacement modalities on amikacin population pharmacokinetics in critically ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother 60:4901–4909
9. Roger C, Wallis SC, Louart B, Lefrant JY, Lipman J, Muller L, Roberts JA (2016) Comparison of equal doses of continuous venovenous haemofiltration and haemodiafiltration on ciprofloxacin population pharmacokinetics in critically ill patients. J Antimicrob Chemother 71:1643–1650
10. Roger C, Muller L, Wallis SC, Louart B, Saissi G, Lipman J, Lefrant JY, Roberts JA (2016) Population pharmacokinetics of linezolid in critically ill patients on renal replacement therapy: comparison of equal doses in continuous venovenous haemofiltration and continuous venovenous haemodiafiltration. J Antimicrob Chemother 71:464–470
11. Ulldemolins M, Soy D, Llaurado-Serra M, Vaquer S, Castro P, Rodriguez AH, Pontes C, Calvo G, Torres A, Martin-Loeches I (2015) Meropenem population pharmacokinetics in critically ill patients with septic shock and continuous renal replacement therapy: influence of residual diuresis on dose requirements. Antimicrob Agents Chemother 59:5520–5528
12. Shotwell MS, Nesbitt R, Madonia PN, Gould ER, Connor MJ, Salem C, Aduroja OA, Amde M, Groszek JJ, Wei P, Taylor ME, Tolwani AJ, Fissell WH (2016) Pharmacokinetics and pharmacodynamics of extended infusion versus short infusion piperacillin-tazobactam in critically ill patients undergoing CRRT. Clin J Am Soc Nephrol 11:1377–1383
13. Jamal JA, Mat-Nor MB, Mohamad-Nor FS, Udy AA, Wallis SC, Lipman J, Roberts JA (2015) Pharmacokinetics of meropenem in critically ill patients receiving continuous venovenous haemofiltration: a randomised controlled trial of continuous infusion versus intermittent bolus administration. Int J Antimicrob Agents 45:41–45
14. Jamal JA, Roberts DM, Udy AA, Mat-Nor MB, Mohamad-Nor FS, Wallis SC, Lipman J, Roberts JA (2015) Pharmacokinetics of piperacillin in critically ill patients receiving continuous venovenous haemofiltration: a randomised controlled trial of continuous infusion versus intermittent bolus administration. Int J Antimicrob Agents 46:39–44
15. Brasseur A, Hites M, Roisin S, Cotton F, Vincent JL, De Backer D, Jacobs F, Taccone FS (2016) A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens: a proof-of-concept study. J Antimicrob Chemother 71:1386–1394