A systematic review of the effect of continuous renal replacement therapy on levetiracetam pharmacokinetics in critically ill patients. Do recommended doses achieve therapeutic drug concentrations?

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Abstract

AIM Levetiracetam is a widely used anti-epileptic in the critical care setting that is almost exclusively (>90%) renally excreted. A significant number of critically unwell patients develop renal failure requiring haemofiltration. This paper investigates the pharmacokinetics of levetiracetam in such patients and the implications on dosing strategies. METHODS A systematic review of the available literature from 2000 was conducted. 7 articles were identified for inclusion from 54 records. A novel hybrid model was used to evaluate the quality of pharmacokinetic and haemofiltration data. Simulations were performed using pooled pharmacokinetic data to evaluate various dosing strategies. RESULTS Total clearance was 3.49 – 4.63L/hr (mean 3.55, S.D. 0.52). Elimination half-life was 5.66 – 12.88 hours (mean 9.41, S.D. 2.86). Volume of distribution was 0.45 – 0.73 L/kg. Levetiracetam clearance from CRRT was 52 – 73% (mean 54.7%, S.D. 13.5). At 72 hours, a significant proportion of simulated patients who received the recommended dose of levetiracetam demonstrated sub-therapeutic drug concentrations. Conversely, the majority who received a standard loading dose (60mg/kg) and twice daily doses in excess of 750mg demonstrated more consistent therapeutic drug concentrations. CONCLUSION Levetiracetam clearance in haemofiltration is similar to healthy adults with normal renal function. The current recommendation to dose as in CKD Stage 3b is likely to result in sub-therapeutic drug concentrations in a high number of patients. A twice daily dosing of 500 – 1,000 mg with an initial loading dose of 60mg/kg should be considered in such patients alongside therapeutic drug monitoring.

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Data Availability Statement	The data that support the findings of this study are available from the corresponding author upon reasonable request.

ABSTRACT

AIM

Levetiracetam is a widely used anti-epileptic in the critical care setting that is almost exclusively (>90%) renally excreted. A significant number of critically unwell patients develop renal failure requiring haemofiltration. This paper investigates the pharmacokinetics of levetiracetam in such patients and the implications on dosing strategies.

METHODS

A systematic review of the available literature from 2000 was conducted. 7 articles were identified for

inclusion from 54 records. A novel hybrid model was used to evaluate the quality of pharmacokinetic and haemofiltration data. Simulations were performed using pooled pharmacokinetic data to evaluate various dosing strategies.

RESULTS

Total clearance was 3.49 – 4.63L/hr (mean 3.55, S.D. 0.52). Elimination half-life was 5.66 – 12.88 hours (mean 9.41, S.D. 2.86). Volume of distribution was 0.45 – 0.73 L/kg. Levetiracetam clearance from CRRT was 52 – 73% (mean 54.7%, S.D. 13.5). At 72 hours, a significant proportion of simulated patients who received the recommended dose of levetiracetam demonstrated sub-therapeutic drug concentrations. Conversely, the majority who received a standard loading dose (60mg/kg) and twice daily doses in excess of 750mg demonstrated more consistent therapeutic drug concentrations.

CONCLUSION

Levetiracetam clearance in haemofiltration is similar to healthy adults with normal renal function. The current recommendation to dose as in CKD Stage 3b is likely to result in sub-therapeutic drug concentrations in a high number of patients. A twice daily dosing of 500 – 1,000 mg with an initial loading dose of 60mg/kg should be considered in such patients alongside therapeutic drug monitoring.

MAIN TEXT

INTRODUCTION

Over the past decade, the use of levetiracetam in critical care settings both in the treatment and prevention of various seizure disorders has significantly increased [**1-2**] . This increase is owed in large part to several studies that have showed it to be a safe, broad-spectrum and highly effective anti-epileptic drug with minimal drug interactions and a wide therapeutic index [**3-5**] . There is no official requirement for therapeutic drug monitoring and, as such, no agreed target range for levetiracetam exists. However, a large scale dose-ranging study conducted among epileptic patients identified a desired therapeutic target of 12 – 46 mcg/mL at trough level[**6**] .

Levetiracetam is a small, hydrophilic molecule that is weakly bound to proteins (<10%) with linear kinetics [**5,7-9**] . In a healthy adult, the total clearance of levetiracetam is approximately 4.03L/hr, the half-life is 6 – 8 hours and the volume of distribution is 0.5 – 0.7L/kg [**10**] . It is almost exclusively (>90%) excreted via the kidneys and so dose adjustments are recommended in patients with impaired renal function[**6,8,11,12**] . Even mild-to-moderate renal impairment has been shown to double plasma concentration and significantly increase drug half-life [**13**] .

Renal impairment is common in critical care settings with around half of people admitted to intensive care developing acute kidney injury[**14-15**] . Continuous renal replacement therapy (CRRT) is used in severe acute kidney injury to support renal function and minimise the risk of multi-organ failure and fluid overload. Additionally, people with end-stage renal disease who require intermittent haemodialysis often benefit from a temporary transition to continuous renal replacement therapy in the event of critical illness due to the enhanced haemodynamic and metabolic control it provides. The introduction of renal replacement therapy creates challenges for pharmacological management as pharmacokinetics are altered through both extrinsic (e.g. filtration mode, filter type, flow rate) and intrinsic factors (e.g. residual renal function, fluid volume status, protein binding). For medications that are renally excreted, such as levetiracetam, the effects on clearance can be significant[**16**] .

Intermittent haemodialysis (IHD) has already been shown to eliminate 50% of levetiracetam within four hours [**13**] . As a result, the current dosing recommendation for patients receiving IHD is a 750mg loading dose followed by 500 – 1,000mg once daily dosing. However, in patients on CRRT the current recommended dosing is 250 – 750mg twice daily without loading – equivalent to a patient with CKD Stage 3b[**17**] . While

there have been a multitude of studies investigating the pharmacokinetics of levetiracetam in haemodialysis to support the current dosing recommendation in IHD **[18-21]** , the evidence base for patients undergoing CRRT remains limited. Indeed, the current dosing recommendations are based on three case reports alone. In the last few years there has been a renewed focus on broadening the evidence base **[22]** .

In this systematic review, we evaluate the latest available evidence on the pharmacokinetics of levetiracetam in critically ill patients undergoing CRRT. This review was performed in light of several case reports and case studies suggesting that the clearance of levetiracetam*in vivo* may be significantly higher than previously thought – raising the risk of sub-therapeusis in such patients**[22-25]** . We undertake a quality assessment of the current evidence in addition to meta-analysis and computational modelling to understand the factors that affect clearance and to simulate the effect of different dosing strategies on plasma concentration.

METHODS

DATA SOURCE AND SEARCHES

The protocol for this systematic review was developed using the PRISMA-P guideline and was registered on PROSPERO (CRD42022300754). Our search strategy is available in **Appendix 1** .

A literature search was conducted in EMBASE, MEDLINE, PubMed and Google Scholar from 2000 to 01 November 2022. The reference lists of selected articles were also checked to identify additional relevant studies for inclusion. An independent search was performed by two authors with a third investigator to resolve any discrepancies.

STUDY SELECTION

All case reports, cohort studies and randomised control trials were included and screened to assess eligibility for inclusion.

A study was eligible for inclusion if it met the following criteria: (1) patients were treated with levetiracetam (regardless of its formulation); (2) patients were undergoing CRRT via continuous veno-venous haemofiltration (CVVHF), continuous veno-venous haemodialysis (CVVHD) or continuous veno-venous haemodiafiltration (CVVHDF). Studies were excluded for the following reasons: (1) it was published in a non-English language; (2) the study was a computational or model-based study not using human patient data; (3) there were insufficient pharmacokinetic data; (4) review article with no additional new pharmacokinetic data.

DATA EXTRACTION AND QUALITY ASSESSMENT

Data were independently extracted from the included studies by two authors (J.S., S.A-M.) using a standardised database. Data extracted included: study design, patient demographics, reason for admission, indications for levetiracetam and CRRT, residual renal function, dosing regimen, CRRT characteristics and settings, and pharmacokinetic data. Any discrepancies on data extraction were arbitrated by a third investigator.

Our quality assessment was performed using a hybrid model that combined the Quality of Evidence (QoE) and Acute Dialysis Quality Initiative (ADQI) scoring systems **[26-28]** . Each study was assessed independently by two authors (J.S., S.A-M.) who allocated separate QoE and ADQI scores as per the protocol detailed in **Appendix 2** . To eliminate discrepancies in ADQI scores between authors, a mean ADQI score was calculated for each study. Overall quality assessment scores were stratified into low, medium and high-quality equivalents based on the average quality of evidence across the QoE and ADQI assessments. For example, a study was ranked medium quality if it achieved a strong QoE score but a weak ADQI score. Any disputes were arbitrated by a third investigator.

DATA SYNTHESIS AND SIMULATION OF DOSING SCENARIOS

Data were collated using Microsoft Excel. Our primary analysis was a mixed narrative and meta-analysis. Descriptive analytics and multiple regression modelling were performed using IBM SPSS Statistics 28. In

cases where specific values were not reported (e.g. ultrafiltration rate, filtration fraction, volume of distribution) these were calculated using the available data and standard formulae where possible. Statistical heterogeneity was not assessed as the Cochrane Q Test and I^2 statistic are not applicable to our dependent variable which is continuous rather than dichotomous.

Simulations were undertaken in R using tidyverse and linpk packages[**29-31**] . Individual patient level data was used for elimination rate constant and volume of distribution. Elimination rate constant was taken directly from published manuscripts or derived from other published pharmacokinetic parameters, where available. Volume of distribution was not available for 8 patients (Chappell). Simulated patients (n=10,000) were created from these values using the MASS package and assuming a multivariate log-normal distribution of parameters [**32**] . For pharmacokinetic profiles, a one compartment model was assumed. Profiles were simulated to 72-hours, on the assumption that steady state would be achieved by then and that this early period of treatment was likely to be the most important in achieving therapeutic concentrations. We utilised a target trough concentration range of 12 – 46 mcg/mL as this is the most widely used therapeutic index [**6, 25, 34, 38**] .

RESULTS

Our search found a total of 58 articles **(Fig. 1)** . Of 54 articles reviewed in full text, seven fulfilled our eligibility criteria for inclusion. Of the included studies, five were case reports[**25,33-36**] and two were prospective pharmacokinetic studies[**37-38**] . In all studies except one (where clinical indication was not recorded) patients were treated with levetiracetam either for known seizures or as prophylaxis (e.g. following traumatic brain injury). In one study [**37**] four patients were treated with SLED and so were excluded from our data extraction.

STUDY CHARACTERISTICS

The characteristics of our included studies are summarised in**Table 1** . In most cases, patients were commenced on CRRT for acute kidney injury or known end-stage renal disease with multi-organ failure. 16 out of 24 patients were treated with CVVHF with 8 other patients treated with CVVHDF. Two patients [**25,34**] were receiving simultaneous extracorporeal membrane oxygenation (ECMO). In most patients (17 out of 24) a 1,000mg twelve-hourly dose of levetiracetam was administered as intravenous bolus infusions. One patient received enteral levetiracetam.

Sampling strategies across studies varied significantly. Pre-filter, post-filter and effluent samples were collected in four studies while in three studies only plasma samples (either peak or trough levels) were taken. In most studies, levetiracetam levels were not taken until steady state had been achieved. One compartmental modelling for pharmacokinetic analysis was used in three studies [**25, 34, 35**] , while Kalaria et. al used a non-compartmental approach.

The recommended delivered dose in CRRT varies but is considered to be between 20 – 35 ml/kg/hr. The median delivered dose in these studies ranged from 26.7 – 37.1 ml/kg/hr with significant variation seen in Chappell et al. and Kalaria et al. Blood flow rates ranged from 180 – 250 ml/min and were broadly consistent across studies. The majority of patients were either anuric or oliguric (defined as urine output <400ml in 24 hours) but it should be noted that these data were not collected by Chappell et al.

PHARMACOKINETIC DATA

Reported levetiracetam clearance from CRRT was between 1.80 – 2.98 L/h (**Table 2**). Where total clearance was calculated, the clearance attributed to CRRT alone was between 52 – 73% (Mean 54.7%, S.D. 13.5). Reported total clearance of levetiracetam was between 3.49 – 4.63L/hr (Mean 3.55, S.D. 0.52). Elimination half-life varied significantly with a range of 5.66 – 12.88 hours and a mean 9.41 hours (S.D. 2.86, S.E. 0.60). Volume of distribution ranged from 0.45 – 0.73 L/kg. In the majority of patients, peak and trough plasma concentrations were within the therapeutic target range of 12 – 46 mcg/mL. The exception to this was in Kalaria et al.'s study in which six patients demonstrated trough plasma concentrations below 12 mcg/mL (1.93 – 9.94 mcg/mL).

STRENGTH OF EVIDENCE

The outcome of our quality assessment is shown in **Table 3** . In general, we determined that the strength of evidence was overall of low quality. The level of information provided about CRRT techniques was broadly inconsistent with few studies providing the level of information required to enable comprehensive interrogation or meta-analysis of the data. In one study **[38]** , demographics were only provided at aggregate level which prevented individualised pharmacokinetic analysis. Time spent on filter was only mentioned in one study **[34]**and while it could be assumed that haemofiltration was continuous, it was clear that at least some patients experienced filter clotting and pauses to treatment. The two prospective studies in our data set**[37, 38]** were judged to be of higher quality predominantly due to the more robust and comprehensive nature of their pharmacokinetic data.

MULTIPLE REGRESSION

Due to a limited base size and various missing data discussed above, it was not possible for us to perform multiple regression analysis with any meaningfully significant results.

SIMULATION OF DOSING SCENARIOS

Figure 2 illustrates the proportion of patients who achieved our therapeutic target level (12 – 46 mcg/mL) across a range of simulated dosing strategies. At a target level of 12 mcg/mL, 65% of simulated patients who received a dose of 1,000 mg every 12 hours achieved target level in comparison to 53% of simulated patients who received 750 mg and 34% of simulated patients who received 500mg.

Table 4 demonstrates the trough concentration profiles at these various simulated doses. At doses <750 mg the median trough concentration was below the target range, although some patients did achieve therapeutic drug concentrations. The exception were patients who received 250 mg – all of whom had trough concentrations below the target level. Even at higher doses ([?]750 mg) some patients still demonstrated trough concentrations below the target level.

Our simulations evaluated levetiracetam concentrations in patients on CRRT receiving a range of doses over a 72-hour period. In **Figure 3** , patients received a standard loading dose of 60mg/kg as recommended for treatment of neurological emergencies **[39-40]** . In**Figure 4** , patients received a 750mg loading dose as recommended for patients on IHD. In **Figure 5** , patients received no loading dose.

As shown in **Figure 3** , the standard loading dose achieved therapeutic drug concentrations within the first 24 hours for almost all simulated patients. Conversely, a significant number of patients who received a reduced (**Fig. 4**) or no loading dose (**Fig. 5**) experienced sub-therapeutic drug concentrations for an extended period – with the majority of patients receiving 250 mg dosing spending the entire 72 hour below target concentration. Only at higher doses (750mg, 1000mg) did median concentrations remain within our target range at 72 hours.

DISCUSSION

Our results demonstrate that the clearance of levetiracetam in critically ill patients undergoing CRRT is consistently demonstrated in the literature to be similar to that seen in healthy adult patients. Both mean total clearance (3.55 L/hr) and elimination half-life (9.41 hrs) were broadly equivalent to that of healthy adults (4.03 L/hr and 6 – 8 hrs respectively). The mean clearance attributable to CRRT was over 50% confirming that CRRT is responsible for the majority of drug clearance. Moreover, it demonstrates that IHD and CRRT have similar pharmacokinetic effects in terms of their ability to eliminate levetiracetam. Taken together, these findings suggest that current dosing recommendations may pose a risk of sub-therapeutic drug concentrations.

Our simulation data also raise several concerns over the current UK dosing recommendations in CRRT, which advise a 250 – 750 mg twice daily regimen without an initial loading dose **[17]** . As demonstrated in **Fig. 5** , without a loading dose the majority of our simulated patients experienced sub-therapeutic drug concentrations for up (and beyond) 72 hours. This effect was reduced to a limited extent with higher

dosing regimens (750 – 1000 mg) but even at higher doses, drug concentrations remained sub-therapeutic for the initial 24 hours of treatment. Even the addition of the loading dose recommended for patients on IHD resulted in the same problem, with the majority of patients experiencing sub-therapeutic drug concentrations up to 24 – 36 hours into treatment (**Fig 4**). The addition of a standard loading dose at 60mg/kg resolved this problem and resulted in the immediate achievement of therapeutic drug concentrations (**Fig. 3**). A significant proportion of patients at this loading dose, however, had trough concentrations over 80 mcg/mL for the first 24 hours and may require additional monitoring for potential drug toxicity[**41**] .

Regular dosing at lower levels (250 – 500mg) was unlikely to achieve therapeutic levels by steady state (**Fig. 3 – 5**). Even with the addition of a loading dose, the median drug concentration for patients receiving these doses remained below 12 mcg/mL at 72 hours. In contrast, at higher doses (750 – 1000mg) a significant number of patients had therapeutic drug concentrations at steady. However, without a standard loading dose of 60mg/kg the time to therapeutic levels (even at higher doses) was delayed by up to 36 hours.

From a pharmacokinetic perspective, these data suggest that current UK dosing recommendations in CRRT are likely to result in extended periods of sub-therapeusis and suggests that patients undergoing CRRT should be considered for a twice daily dosing of 500 – 1,000 mg in addition to an initial loading dose of 60mg/kg. A major limitation of this work is the lack of data on efficacy or the use of the target trough concentration in the critically ill cohort. However, given the relatively low event rate of seizures, the relatively low number of patients receiving the drug whilst also receiving renal replacement therapy and the number patients receiving this drug for prophylaxis, it is highly unlikely in our view that a PK-PD trial will be realised.

The specific extrinsic factors related to CRRT, such as effluent flow rate or dialysate rate, that influence levetiracetam clearance remain unclear. Few studies investigated the haemofiltration characteristics that influence clearance with the exception of Kalaria et al. Their analysis identified effluent flow rate and sieving co-efficient as the main influences on clearance. Effluent rates in excess of 3.5L/h were also associated with increased clearance and so higher doses may be required in these patients.

Similarly, further investigation into the intrinsic patient-specific factors that affect clearance is also required. While mean clearance was consistent between studies, there was a wide variation in individual patient clearance and plasma concentrations which are not easily explained by effluent rate and sieving co-efficient alone. Six patients demonstrated trough drug concentrations below the therapeutic target level but a post-hoc descriptive analysis (**Appendix 3**) found no obvious explanation. Three of these patients had significant residual urine output (>300ml per day), while three others had high effluent rates. However, other patients received similar doses at higher effluent rates or indeed had higher urine outputs without their plasma concentrations falling outside of target levels. These data suggest that there is a high inter-person variability of drug pharmacokinetics and determining optimum dosing strategies for individuals may require therapeutic drug monitoring.

Finally, our systematic review illustrates that the availability of pharmacokinetic data on levetiracetam in CRRT remains limited. Data are limited to a small number of case reports and two small prospective studies. There is a lack of consistency between studies, both in terms of methodology and data reporting, that further limits the overall evidence base at present. In this paper, we have introduced a novel quality assessment method that utilises a combination of the QoE framework, which assesses the strength of pharmacokinetic studies based on the quality of data and pharmacokinetic modelling provided, and the ADQI minimum reporting criteria, which was developed to standardise comparisons between studies that reported on CRRT techniques. Both methods have been used in similar systematic reviews in this way[**42, 43**] but never before in combination. By combining these assessment methods, our quality assessment method allows for equal consideration of both the pharmacokinetic and haemofiltration data. This enables an assessment of both the quality of the data itself and the ability to perform meta-analysis.

Further study is required in order to understand the high inter-person variability in levetiracetam clearance and the *in vivo* effects of different dosing strategies. Such data can be used to develop pharmacokinetic

models that will enable clinicians to determine patient-specific dosing strategies. Future *in vivo* studies should prioritise the collection of standardised data to facilitate meta-analysis and modelling. Our recommendation is that this should include the ADQI minimum reporting criteria alongside the following: (1) IBW; (2) urine output; (3) baseline bloods (albumin, creatinine, haematocrit, liver function); (4) dosing strategy; (5) a sampling strategy that at a minimum includes pre-filter, post-filter and effluent levels; (6) information on whether seizures were controlled or uncontrolled. Standardisation will enable more robust modelling than is possible at present.

In addition to *in vivo* studies, experimental study using lab-based models that simulate critically ill patients undergoing CRRT may be valuable. These studies, such as the latest ex-vivo in-vivo study by Kalaria et al. [**44**] , would be useful in evaluating the effects on clearance of different CRRT parameters and levetiracetam dosing without the potential risk of exposing patients to possible sub-therapeutic or toxic drug levels.

CONCLUSIONS

The available data on *in vivo* clearance of levetiracetam in critically ill patients undergoing CRRT does not support dose reduction in these patients. Clearance is consistently demonstrated to be similar to healthy adults with normal renal function. The current recommendation to dose as in CKD3b is likely to result in sub-therapeutic drug concentrations in a high number of patients. A lack of consensus on a therapeutic window for levetiracetam makes dosing recommendations challenging. However, given the similarities in clearance between CRRT and IHD we would recommend considering a twice daily dosing of 500 – 1,000 mg with an initial loading dose of 60mg/kg. Therapeutic drug monitoring should be used to guide dosing and identify those at risk of toxicity.

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CONFLICTS OF INTEREST

The authors declare no special interests or conflicts of interest.

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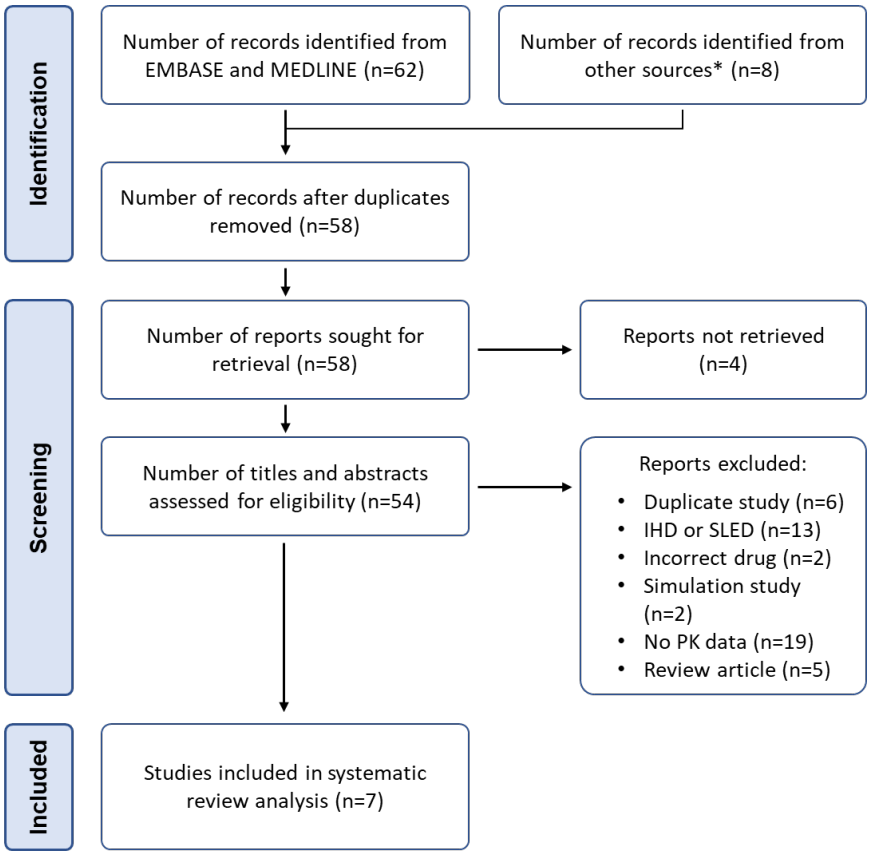
REFERENCES

1. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004;62(8):1252–60.
2. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17(1):3–23.
3. De Smedt T, Raedt R, Vonck K, Boon P. Levetiracetam: the profile of a novel anticonvulsant drug-part I: preclinical data. CNS Drug Rev. 2007 Spring;13(1):43-56. Doi: 10.1111/j.1527-3458.2007.00004.x.
4. Nau KM, Divertie GD, Valentino AK, Freeman WD: Safety and efficacy of levetiracetam for critically ill patients with seizures. Neurocrit Care, 2009; 11(1): 34–37.
5. Patsalos, P. (2000) 'Pharmacokinetic profile of levetiracetam toward ideal characteristics.', Pharmacology & Therapeutics, 85, pp.77-85.
6. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE commission on therapeutic strategies. Epilepsia 2008;49:1239–76. https://doi.org/ 10.1111/j.1528-1167.2008.01561.x

7. Radtke, R.A. (2001), Pharmacokinetics of Levetiracetam. Epilepsia, 42: 24-27.*https://doi.org/10.1111/j.1528-1167.2001.00005.*
8. Patsalos PN: Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet, 2004; 43(11): 707–24.
9. Walker MC, Patsalos PN: Clinical pharmacokinetics of new antiepileptic drugs. Pharmacol Ther, 1995; 67(3): 351–84.
10. DrugBank. Levetiracetam. Available at: https://go.drugbank.com/drugs/DB01202 (Accessed: 16 December 2021).
11. EMC. *Keppra 100 mg/ml concentrate for solution for infusion* . Available at:*https://www.medicines.org.uk/emc/product/2296/smpc#PHARMACOKINETIC_-PROPS*(Accessed: 8 December 2021).
12. Strolin Benedetti M, Whomsley R, Nicolas J-M, Young C, Baltes E. Pharmacokinetics and metabolism of 14C-levetiracetam, a new antiepileptic agent, in healthy volunteers. Eur J Clin Pharmacol. 2003;59(8–9):621–30.
13. Mora Rodríguez KA, Benbadis SR. Managing Antiepileptic Medication in Dialysis Patients. Curr Treat Options Neurol. 2018 Sep 27;20(11):45. doi: 10.1007/s11940-018-0530-5. PMID: 30259204.
14. Tolwani A: Continuous renal-replacement therapy for acute kidney injury. New Engl J Med, 2012; 367(26): 2505–14.
15. Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract. 2013;2013:479730. doi: 10.1155/2013/479730. Epub 2013 Mar 21. PMID: 23573420; PMCID: PMC3618922.
16. Schetz M: Drug dosing in continuous renal replacement therapy: General rules. Curr Opin Crit Care, 2007; 13(6): 645–51.
17. Ashley, C. and Dunleavy, A. The Renal Drug Database. Available at: https://renaldrugdatabase.com/ (Accessed: 13 April 2023).
18. Shiue HJ, Taylor M, Sands KA. Comparison of Levetiracetam Dosing Regimens in End-Stage Renal Disease Patients Undergoing Intermittent Hemodialysis. Ann Pharmacother. 2017;51(10):862-865. doi:10.1177/1060028017713294, 10.1177/1060028017713294
19. Wieruszewski PM, Kashani KB, Rabinstein AA, Frazee E. Levetiracetam Pharmacokinetics in a Critically Ill Anephric Patient on Intermittent Hemodialysis. Neurocrit Care. 2018;28(2):243-246. doi:10.1007/s12028-017-0441-4, 10.1007/s12028-017-0441-4.
20. Smetana KS, Cook AM, Bastin ML, Oyler DR. Antiepileptic dosing for critically ill adult patients receiving renal replacement therapy. J Crit Care. 2016;36:116-124. doi:10.1016/j.jcrc.2016.06.023, 10.1016/j.jcrc.2016.06.023.
21. Rodriguez, K. and Benbadis, S. (2018) 'Managing Antiepileptic Medication in Dialysis Patients', Current Treatment Options in Neurology, 20:45.
22. Cuhls, M., Bosel, J. and Rosche, J. (2020) 'Treatment with lacosamide or levetiracetam in patients with renal replacement therapy. What is really known?', *Journal of Epileptology* , 28, pp.55-58.
23. Araki, K. et al. (2020) 'Pharmacological monitoring of antiepileptic drugs in epilepsy patients on haemodialysis.', *Epileptic Disorders* , 22(1), pp. 90-102.
24. Maia, J. et al. (2008) 'Effect of renal impairment on the pharmacokinetics of eslicarbazepine acetate.', *International Journal of Clinical Pharmacology & Therapeutics* , 46(3), pp.119-30.
25. Nei, SD. et al. (2015) 'Levetiracetam Pharmacokinetics in a Patient Receiving Continuous Venovenous Hemofiltration and Venoarterial Extracorporeal Membrane Oxygenation.', *Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy* , 35(8), pp.127-30.
26. Barker CI, Standing JF, Turner MA, et al. Antibiotic dosing in children in Europe: can we grade the evidence from pharmacokinetic/ pharmacodynamic studies - and when is enough data enough? Curr Opin Infect Dis. 2012 June;25(3):235–242.
27. Gibney RT, Kimmel PL, Lazarus M. The Acute Dialysis Quality Initiative–part I: definitions and reporting of CRRT techniques. Adv Ren Replace Ther. 2002 Oct;9(4):252-4. doi: 10.1053/jarr.2002.35571. PMID: 12382226.
28. Kellum JA, Mehta RL, Angus DC, Palevsky P, Ronco C, ADQI Workgroup. The first international

consensus conference on continuous renal replacement therapy. Kidney Int 2002; 62: 1855–63.
29. R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/
30. Wickham et al., (2019). Welcome to the tidyverse. Journal of Open Source Software, 4(43), 1686. DOI: https://doi.org/10.21105/joss.01686
31. Rich B (2021). _linpk: Generate Concentration-Time Profiles from Linear PK Systems_. R package version 1.1.1. URL: https://CRAN.R-project.org/package=linpk
32. Venables N. and Ripley B.D. (2002) Modern Applied Statistics with S. Fourth Edition. Springer, New York. ISBN 0-387-95457-0.
33. le Noble JL, Foudraine NA, Kornips FH, van Dam DG, Neef C, Janssen PK. Extracorporeal Clearance of Levetiracetam During Continuous Venovenous Hemofiltration in a Critically Ill Patient and New Dosing Recommendation. J Clin Pharmacol. 2017 Apr;57(4):536-537. doi: 10.1002/jcph.844. Epub 2016 Nov 21. PMID: 27868207.
34. New AM, Nei SD, Kashani KB, Rabinstein AA, Frazee EN. Levetiracetam Pharmacokinetics During Continuous Venovenous Hemofiltration and Acute Liver Dysfunction. Neurocrit Care. 2016 Aug;25(1):141-4. doi: 10.1007/s12028-016-0242-1. PMID: 26800696.
35. Van Matre ET, Mueller SW, Fish DN, MacLaren R, Cava LF, Neumann RT, Kiser TH. Levetiracetam Pharmacokinetics in a Patient with Intracranial Hemorrhage Undergoing Continuous Veno-Venous Hemofiltration. Am J Case Rep. 2017 Apr 27;18:458-462. doi: 10.12659/ajcr.902709. PMID: 28446744; PMCID: PMC5414484.
36. Louie JM, Raphael KL, Barker B. Levetiracetam Use With Continuous Renal Replacement Therapy. Ann Pharmacother. 2015 Sep;49(9):1079-80. doi: 10.1177/1060028015591845. Epub 2015 Jun 23. PMID: 26104053.
37. Chappell K, Kimmons LA, Haller JT, Canada RB, He H, Hudson JQ. Levetiracetam pharmacokinetics in critically ill patients undergoing renal replacement therapy. J Crit Care. 2021 Feb;61:216-220. doi: 10.1016/j.jcrc.2020.10.032. Epub 2020 Nov 2. PMID: 33217623.
38. Kalaria SN, Armahizer M, McCarthy P, Badjatia N, Gobburu JV, Gopalakrishnan M. A Practice-Based, Clinical Pharmacokinetic Study to Inform Levetiracetam Dosing in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration (PADRE-01). Clin Transl Sci. 2020 Sep;13(5):950-959. doi: 10.1111/cts.12782. Epub 2020 Apr 3. PMID: 32223067; PMCID: PMC7485952.
39. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, Shinnar S, Conwit R, Meinzer C, Cock H, Fountain N, Connor JT, Silbergleit R; NETT and PECARN Investigators. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med. 2019 Nov 28;381(22):2103-2113. doi: 10.1056/NEJMoa1905795.
40. Haller JT, Bonnin S, Radosevich J. Rapid administration of undiluted intravenous levetiracetam. Epilepsia. 2021 Aug;62(8):1865-1870. doi: 10.1111/epi.16961. Epub 2021 Jun 24. PMID: 34164804.
41. Wood KE, Palmer KL, Krasowski MD. Correlation of elevated lamotrigine and levetiracetam serum/plasma levels with toxicity: A long-term retrospective review at an academic medical center. Toxicol Rep. 2021 Aug 30;8:1592-1598. doi: 10.1016/j.toxrep.2021.08.005. PMID: 34522622; PMCID: PMC8424104.
42. Silke Gastine, Asia N. Rashed, Yingfen Hsia, Charlotte Jackson, Charlotte I. S. Barker, Shrey Mathur, Stephen Tomlin, Irja Lutsar, Julia Bielicki, Joseph F. Standing & Mike Sharland (2019) GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies) a critical appraisal system for antimicrobial PKPD studies – development and application in pediatric antibiotic studies, Expert Review of Clinical Pharmacology, 12:12, 1091-1098, DOI: *10.1080/17512433.2019.1695600*.
43. Vaara S, Pettila V, Kaukonen KM. Quality of pharmacokinetic studies in critically ill patients receiving continuous renal replacement therapy. Acta Anaesthesiol Scand. 2012 Feb;56(2):147-57. doi: 10.1111/j.1399-6576.2011.02571.x. Epub 2011 Oct 19. PMID: 22092254.
44. Kalaria, S.N., Armahizer, M., McCarthy, P. et al. Development and Use of an Ex-Vivo In-Vivo Correlation to Predict Antiepileptic Drug Clearance in Patients Undergoing Continuous Renal Replacement Therapy. Pharm Res 39, 827–836 (2022). https://doi.org/10.1007/s11095-022-03287-x.

TABLES AND FIGURES



* Other sources searched included PubMed, Google Scholar and reference lists.

FIGURE 1: PRISMA flow chart for study inclusion.

TABLE 1: Characteristics of studies included within systematic review.

Study	Study Type	No. of subjects	Assay Method	Sampling Strategy	Age Mean ± SD [range]	Weight (kg) Mean ± SD [range]	Loading Dose Mean ± SD [range]	Daily Dose Median ± SD [range]	Administration Route
Chappell et al. (2020) [37]	Prospective PK study	8	LC-MS/MS *	Pre-filter plasma; post-filer plasma; effluent [1]	53 ± 15.5 [31 – 71]	85 ± 18.2 [62 – 125]	-	1,000mg every 12 hours [500 – 2,000]	Intravenous
Kalaria et al. (2020) [38]	Prospective PK study	11	LC-MS/MS *	Pre-filter plasma; post-filter plasma; effluent [2]	63.8 ± 13.2 [-]	95.7 ± 15.8 [-]	-	1,000mg every 12 hours [500 – 2,000]	Intravenous (n=10); Oral (n=1)
le Noble et al. (2017) [33]	Case report	1	RP-HPLC ᵠ	Pre-filter plasma; post-filter plasma; blood plasma; effluent	79	90	-	1,000mg every 12 hours	Intravenous
Louie et al. (2015) [36]	Case report	1	Enzyme immunoassay	Trough plasma levels [3]	51	-	500mg	1,000mg every 12 hours	Intravenous
Nei et al. (2015) [25]	Case report	1	LC-MS/MS *	Peak (1h post-infusion) and trough (15 mins pre-infusion) plasma levels	67	116.9	2000mg	1,000mg every 12 hours	Intravenous
New et al. (2016) [34]	Case report	1	LC-MS/MS *	Trough (15 mins pre-dose) plasma level [4]	59	93.2	-	1,000mg every 12 hours	Intravenous
Van Matre et al. (2017) [35]	Case report	1	LC-MS/MS *	Pre-filter plasma; post-filter plasma; effluent; 12h urine collection [5]	78	93.2	-	1,000mg every 12 hours	Intravenous

* Liquid chromatography-tandem mass spectrometry. ᵠ Reversed-phase high-performance liquid chromatography.
[1] Taken at 0, 2, 4 and 6 hours (timings unrelated to dose) for all but effluent samples which were taken at specific but undefined times.
[2] Taken pre-dose, after infusion or 1h post-oral administration and at six additional time points post administration.
[3] Performed after dose 4, 5 and 9.
[4] Performed after the fourth dose only.
[5] Taken at 2, 4, 6, 8 and 10 hours after administration.

TABLE 1: Continued.

Study	CRRT Modality	Filter Type	Delivered Dose (ml/kg/hr) ᵠ	Q_b (mL/min) ᵠ	Q_{eff} (mL/hour) ᵠ	FF (%) ᵠ	Residual Urine Output (mL/kg/hr)
Chappell et al. (2020) [37]	CVVHDF (n=7); CVVHF (n=1)	HF1400	27 ± 9.3 [19 – 53]	200 ± 26.9 [180 – 250]	2,500 ± 5978 [1,700 – 3,575]	28%	-
Kalaria et al. (2020) [38]	CVVHF (n=11)	AN69HF	25 ± 7.6 [22 – 44]	200 ± 50.8 [100 – 250]	2,700 ± 730.4 [2,100 – 4,200]	27%	0.16 ± 0.15 [0.00 – 0.39]
le Noble et al. (2017) [33]	CVVHF	AN69ST	37.1	180	3,336	39%	0.00
Louie et al. (2015) [36]	CVVHDF	AN69	-	-	-	-	0.00
Nei et al. (2015) [25]	CVVHF	HF1400	27.0	200	3,156	34%	0.00
New et al. (2016) [34]	CVVHF	HF1400	28.9	200	2,693	35%	0.00
Van Matre et al. (2017) [35]	CVVHF	High-flux polyethersulfone membrane	26.7	250	2,488	21%	0.07

ᵠ Median ± S.D.
Q_b = Blood flow rate. Q_{eff} = Effluent Flow Rate. FF = Filtration Fraction.

TABLE 2: Levetiracetam pharmacokinetic data from included studies.

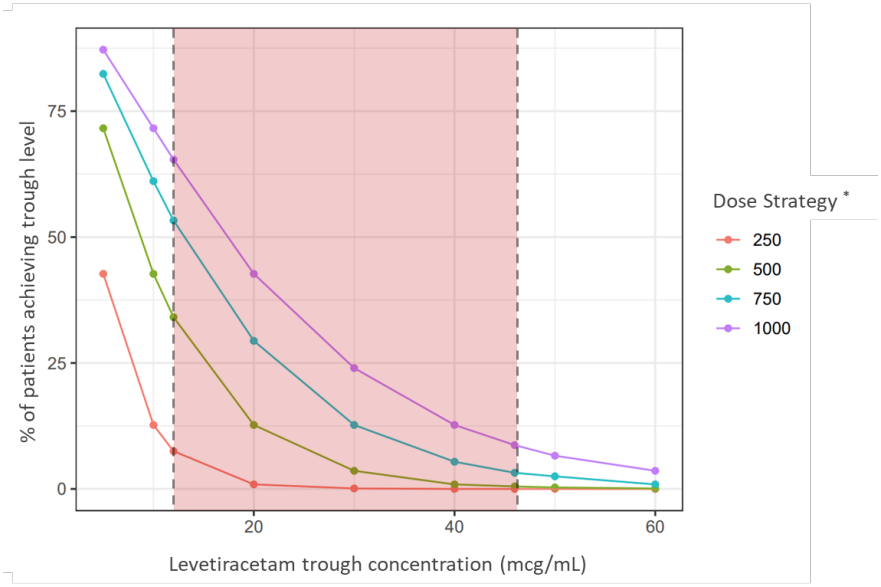
Study	C_{max} (mcg/mL)	C_{min} (mcg/mL)	CL_{TOTAL} (L/h)	CL_{CVVH} (L/h)	CL_{CVVH} (%)	LEV ke (h^{-1})	LEV $t_{1/2}$ (h)	SC	Vd (L)	Vd (L/kg)
Chappell et al. (2020) [37] *	-	-	-	1.80 ± 0.41 [1.35 – 2.42]	-	0.07 ± 0.01 [0.05 – 0.09]	10.28 ± 3.69 [7.60 – 12.90]	0.78 ± 0.08 [0.65 – 0.88]	-	-
Kalaria et al. (2020) [38] *	37.76 ± 39.97 [14.86 – 81.34]	13.32 ± 15.73 ᵀ [1.93 – 34.72]	3.49 ± 6.80 [2.66– 4.35]	2.06 ± 0.32 [1.29 – 3.24]	52.40 ± 13.29 [35.90 – 72.80]	0.08 ± 0.05 [0.04 – 0.17]	8.48 ± 3.69 [2.58 – 13.24]	0.89 ± 0.13 [0.80 – 1.08]	51.64 ± 23.30 [13.15 – 85.47]	0.73 ᵠ
le Noble et al. (2017) [33]	41.20	-	4.07	2.98	73.05	0.12	5.66	0.89	40.5	0.45
Louie et al. (2015) [36]	19.00	-	-	-	-	-	-	-	-	-
Nei et al. (2015) [25]	32.06	15.90	4.63	-	-	0.07	9.42	-	76.0	0.65
New et al. (2016) [34]	32.20	16.10	3.71	-	-	0.06	11.40	-	60.8	0.65
Van Matre et al. (2017) [35]	30.70	16.10	3.68	2.25	61.30	0.05	12.88	1.03	68.3	0.73

* Data have been summarised as mean ± S.D. [range] for studies where multiple participants were investigated.
ᵀ Based on predicted Cmin rather than observed values.
ᵠ Mean of the individual patient Vd (L/kg) based on actual patient weight.

TABLE 3: Outcomes from quality assessment of included reports.

Study	Quality of Evidence (QoE) Score	Acute Dialysis Quality Initiative (ADQI) Score	Overall Quality Assessment
Chappell et al. (2020) [37]	Strong	4.3	Medium Quality
Kalaria et al. (2020) [38]	Strong	5.0	High Quality
le Noble et al. (2017) [33]	Weak	8.8	Low Quality
Louie et al. (2015) [36]	Weak	4.0	Low Quality
Nei et al. (2015) [25]	Weak	8.8	Low Quality
New et al. (2016) [34]	Weak	8.0	Low Quality
Van Matre et al. (2017) [35]	Weak	6.5	Low Quality

FIGURE 2: Percentage of simulated patients achieving trough concentrations based on various dosing strategies.



* Dosing strategies are based on 12 hourly administration of levetiracetam with no loading dose.
Shaded border indicates our therapeutic target range of 12 – 46 mcg/mL.

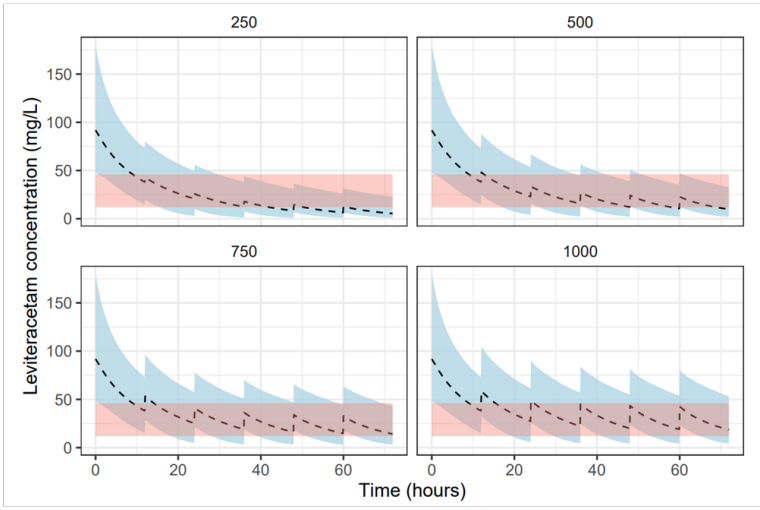
TABLE 4: Trough concentration profile for a range of simulated levetiracetam doses during continuous renal replacement therapy.

	Levetiracetam dose (mg)			
	250	**500**	**750**	**1000**
Cmin (mg/L)	4 (1-11)	9 (2-22)	13 (3-33)	17 (4-44)

[1] Median (10%-90%)

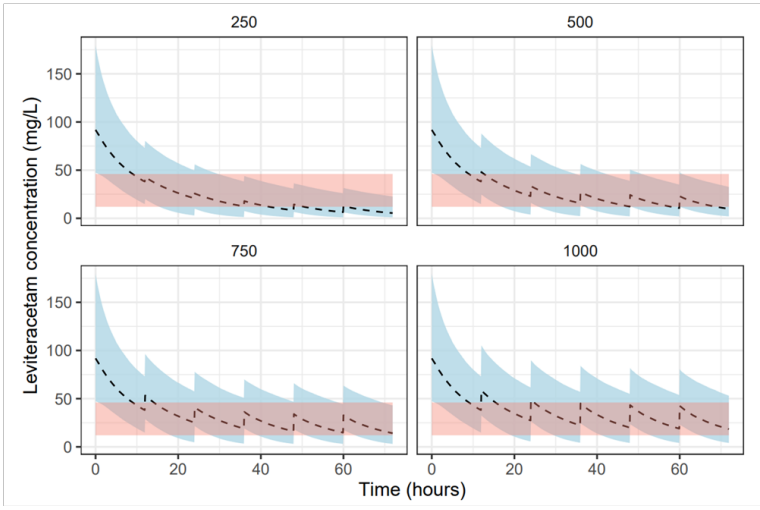
Dosing strategies are based on 12 hourly administration of levetiracetam with no loading dose.

FIGURE 3: Pharmacokinetic profile for a range of levetiracetam doses with **60mg/kg loading dose** in simulated patients receiving renal replacement therapy.



Simulations received a 12-hrly dose **with an initial 4.5g loading dose** as indicated on each panel. This assumed a 75kg adult patient with a loading dose of 60mg/kg. Dotted line shows median simulated concentration profile with surrounding blue shaded area representing 10th to 90th centile. Horizontal shaded area represents the range of therapeutic trough concentrations (12 - 46 mcg/mL).

FIGURE 3: Pharmacokinetic profile for a range of levetiracetam doses with **60mg/kg loading dose** in simulated patients receiving renal replacement therapy.



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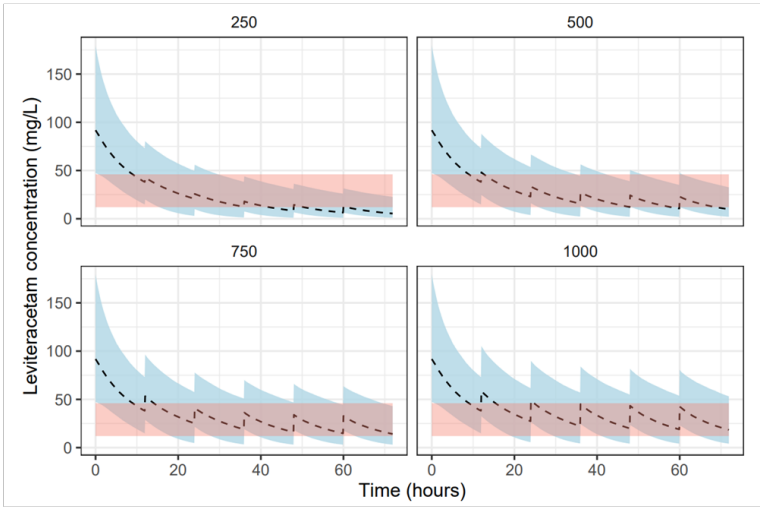

Simulations received a 12-hrly dose **with an initial 4.5g loading dose** as indicated on each panel. This assumed a 75kg adult patient with a loading dose of 60mg/kg. Dotted line shows median simulated concentration profile with surrounding blue shaded area representing 10th to 90th centile. Horizontal shaded area represents the range of therapeutic trough concentrations (12 - 46 mcg/mL).

APPENDICES

APPENDIX 1: SEARCH CRITERIA

Database: Embase <1996 to 2022 Week 02>

Search Strategy:

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1 (levetiracetam or keppra).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (16748)

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3 1 or 2 (16748)

4 h#emodialysis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (17934)

5 h#emofiltration.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1190)

6 (continuous renal replacement or continuous renal replacement therapy or CRRT*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (9078)

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16 11 or 12 or 13 or 14 or 15 (4417124)

17 3 and 10 and 16 (58)

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Database: Ovid MEDLINE(R) ALL <1946 to January 26, 2022>

Search Strategy:

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8 exp Continuous Renal Replacement Therapy/ (460)

9 dos*.mp. (2974912)

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12 exp Pharmacokinetics/ (327036)

13 1 or 2 (4712)

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15 9 or 10 or 11 or 12 (5989859)

16 13 and 14 and 15 (21)

17 limit 16 to (english language and yr="2000 -Current") (20)

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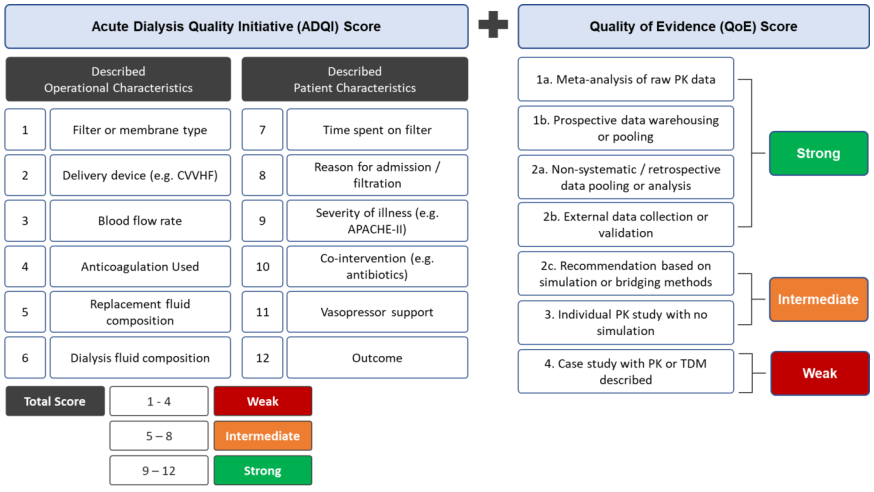
APPENDIX 2: Detailed framework of our hybrid Quality Assessment Method.



APPENDIX 2: Detailed framework of our hybrid Quality Assessment Method.

APPENDIX 3: Ad-hoc analysis of patients with sub-therapeutic drug concentrations.

APPENDIX 3: Ad-hoc analysis of patients with sub-therapeutic drug concentrations.

Patient ID	C_{min} (mcg/mL)	LEV Dose (mg)	24 Hour Urine Output (mL)	Delivered Dose (ml/kg/hr)	Q_{eff} (mL/hour)	CL_{TOTAL} (L/h)	CL_{CVVH} (L/h)	CL_{CVVH} (%)	LEV ke (h^{-1})	SC
ID001	1.9	750	332	24.0	2300	58.5	33.3	51.3	0.266	1.08
ID002	7.2	1000	160	21.9	2100	44.3	21.5	36.4	0.269	0.80
ID003	9.9	1000	175	32.4	3100	58.2	32.8	35.9	0.067	0.80
ID004	11.4	1000	0	43.9	4200	72.5	54.0	72.8	0.074	0.90
ID005	6.4	500	613	21.9	2100	53.5	28.0	43.5	0.065	0.88
ID006	8.0	1000	1089	32.9	3150	67.5	42.3	49.1	0.110	0.93
MEDIAN	**14.8**	**1000**	**151**	**28.2**	**2700**	**59.7**	**33.3**	**51.3**	**0.070**	**0.88**
MAX	**34.7**	**2000**	**1089**	**52.5**	**4200**	**77.2**	**54.0**	**73.1**	**0.270**	**1.08**
MIN	**1.9**	**500**	**0**	**19.0**	**1700**	**44.3**	**21.5**	**35.9**	**0.050**	**0.65**

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