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# Intensive Care Unit Renal Replacement Therapy: Less Is More (or Better)

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EDITORIAL

# Intensive Care Unit Renal Replacement Therapy: Less Is More (or Better)

Acute kidney injury (AKI) is on every nephrologist's mind. Although it took some time for the transition to the nomenclature of CKD stages from chronic kidney failure, the rapid assimilation of "AKI" into the internal medicine vernacular has been relatively light speed. Now, AKI must be considered a cause of CKD, although not necessarily in the fashion of a 5/6 nephrectomy—an immediate cause of CKD that is accompanied by a tremendous degree of compensatory hypertrophy unseen in the human analogue. In a retrospective analysis of hospitalized veterans by Heung and colleagues,[1] AKI that is not of prerenal origin was associated with residual kidney damage and CKD, defined as CKD Stage 3 or greater 1-year postdischarge. The individuals who recovered more quickly, with recovery defined as a predischarge serum creatinine within 0.3 mg/dL of the baseline serum creatinine, demonstrated improved outcomes. Older patients fared less well, as expected, which is clinically relevant given that the elderly population is an increasingly larger proportion of intensive care unit admissions. Bagshaw et al.[2] calculate that the rate of adults aged 80 years and older admitted to intensive care units will increase by 72% by 2015, equaling nearly one-quarter of such admissions.

In this issue of "Advances in Chronic Kidney Disease", our Associate Editor, Kathleen Liu serving as guest editor with her colleague, Michael Connor, brings forth a series of newer ideas that the nephrologist–intensivist can use to improve the care of critically ill individuals with AKI. Undoubtedly, some of the concepts and innovations described by her talented group of authors will be embraced and used by not only today's current nephrologists but also by the future nephrologists currently in training. In brief, we can do more for our AKI patients by doing more. However, we can also accomplish more by doing less.

With the advent of continuous renal replacement therapies, the dose of dialysis administered to ICU patients has increased. Now, there is the concept of "renal support therapy" vs renal replacement therapy (RRT), that is, nephrologists assist the intensivist by conducting ultrafiltration and/or dialysis far more than previously.[3] Historically, due to the lack of an ultrafiltration meter situated on the dialysis machine, transmembrane pressures were calculated, usually by the dialysis nurse, to approximate the total ultrafiltration. This estimation proved sufficient in most circumstances, but was supplanted by technology that permitted one to "dial in" ultrafiltration rates and volumes. Consequently, nephrologists are able to remove large volumes of ultrafiltrate, thereby avoiding "fluid overload (FO)," a term that implies pathophysiological distinction from heart failure with pulmonary edema, although it is not. Avoiding FO of 10% or greater is an evidence-based target as excessive fluid administration is associated with higher mortality and greater ventilator days and ICU length of stays.[4,5] This was established much earlier than appreciated by Mitchell and colleagues[6] nearly a quarter-decade ago in a randomized, prospective study.

Nonetheless, the ability of physicians to overload a patient with fluid to greater than 10% of admission weight with a panoply of salt-containing solutions remains unfettered. First, the solution for fluid resuscitation makes little difference clinically, but it does monetarily. Saline has not been proven inferior to either buffered saline solutions or more expensive oncotic solutions of albumin, although the jury is still out on this. However, excessive volume administrations of saline can obfuscate a diagnosis of AKI by dilution and induce a hyperchloremic metabolic acidosis. The electronic health records of patients maintain fluid logs that are easily graphed and reported, but no warning system exists when the 10% FO threshold is reached and subsequently surpassed, at which time the nephrologist is consulted for renal replacement and/or support therapy. More easily, a limitation on intravenous and other routes of fluid administration should have been imposed. When hemodynamic resuscitation is an ongoing requirement,


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augmenting vasopressor support vs increasing fluids is the better choice because more fluids foster more renal support therapy, which devolves into a never-ending cycle. The ongoing fluid administration promotes more continuous renal replacement therapy (CRRT), either long-term dialysis with sustained low-efficiency daily dialysis or continuous venovenous hemofiltration (CVVH), with or without hemodialysis (CVVHD). This fluid overloading process can be stopped by "early goal–directed thinking," which constitutes establishing an FO threshold target of 10% and developing electronic warning systems that facilitate reduction of fluid administration. Notably, no fluid-logging system of any electronic health record distinguishes between the electrolyte-containing and electrolyte-free proportions of a solution. This coalescence of fluids into a single fluid on a flow sheet consequently generates errant estimates of the volume of fluid that should undergo ultrafiltration, that is, only the isotonic volume of fluid should undergo ultrafiltration, with residual tonicity problems evaluated and managed separately.

Prolonged RRT has been misused and has its disadvantages. High-effluent volume removal (35 mL/kg/h) was accorded primacy by devotees of CRRT, as this would promote cytokine removal and potentially mitigate inflammation during sepsis-induced AKI. Sustaining such an effluent rate is a formidable task and requires time, effort, and vigilance. With the benefit of data from 2 large, multicenter, randomized, controlled trials, a lesser effluent dose is recommended.[7,8] The results of the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN; $n = 1124$) study[7] and the Randomized Evaluation of Normal vs Augmented Level ($n = 1508$) Replacement Therapy Study[8] have yielded level 1 evidence that effluent flow rates above 25 mL/kg/h do not provide better outcomes in patients in the ICU. The provision of higher effluent rates for improved outcomes in sepsis-induced AKI vis-a-vis cytokine removal also remains unproven,[9] and further research into cytokine adsorption during RRT or in isolation is required.[10]

The KDIGO recommendation for more conventional hemofiltration rates of 20 to 25 mL/kg/h[9] is fortunate because it precludes in part the ongoing potassium, magnesium, and phosphate losses that occur with prolonged hemofiltration or dialysis. Cardiac arrhythmias and skeletal muscle weakness are the consequences of any of these problems, and should these deficits occur in concert, disaster awaits. Hypophosphatemia is associated in ventilator patients with a failure-to-wean.[11] Phosphate transfer during an intermittent hemodialysis session was less than half of that occurring during a 24-hour CRRT treatment, despite a 4-fold higher clearance with hemodialysis.[12] The phosphate deficit can be dispatched by using a phosphate-containing dialysate,[13] and there is no commercially equivalent solution available in the United States, although a pre-mixed phosphate-containing CRRT replacement solution is available (Phoxillum, Baxter). Alternatively, a concocted sodium/potassium phosphate dialysate is possible. Finally, sodium glycerophosphate pentahydrate could be used, especially in the face of a pharmacy-based phosphate supply problem. Due to the inexperience of most practitioners directly manipulating the dialysate, most clinicians opt to infuse one of these solutions, but this strategy requires greater frequency of monitoring than a fixed phosphate concentration dialysate.

In addition, there may be renal trauma induced by overly ambitious effluent rates. Maynar-Molinar and colleagues[14] recently coined the term, "dialytrauma," which more comprehensively speaks to the less well-perceived negative effects of continuous renal replacement treatment.[15] A partial listing of these traumatic events includes the aforementioned electrolyte and mineral disturbances, caloric loss through heat dissipation, carbohydrates, nitrogen, water-soluble vitamins, trace elements, and drugs, particularly antibiotic agents. In this vein, Lewis and Mueller[16] previously demonstrated the requirement for greater antibiotic doses during CRRT because prevailing antibiotic levels were lower than the threshold for a bactericidal effect. Levels were less than optimal attributable to prolonged hemofiltration and other reasons, including improved hepatic clearance in AKI patients (compared with ESRD patients) and variability in body habitus and fluid composition of patients undergoing CRRT. Clinicians were warned against antibiotic conservatism: antibiotic dosing should be aggressively administered to vulnerable, critically ill patients treated with CRRT. This warning is a clarion call for greater research involving not only antibiotics and other commonly used agents in ICU patients. Even the pharmacokinetics and pharmacodynamics of commonly used vasopressors are not well described during sustained low-efficiency daily dialysis (SLED) or CVVH(D). Commonly used vasopressors are dialyzable, but dose adjustments are rarely made for patients undergoing CVVH(D) or SLED. However, Honoré and colleagues[15] contend that "CRRT is not a 'hurdle' for adequate antimicrobial dosing but rather a 'shield' allowing higher antimicrobial dosing at less toxicity risk." They state that although CRRT is a technique that promotes antimicrobial underdosing, it simultaneously facilitates the administration of higher antibiotic doses of *per se* amikacin and colistin with a lesser risk for nephrotoxicity.[15,17]

Slavish adherence to a fixed dialysis schedule for hospitalized patients potentially injures them or at best provides no benefit. The excessive clearance of "uremic solutes" has not been shown to provide superior outcomes, if one extrapolates outpatient kinetic data to inpatients.[18] If a patient is not hypercatabolic and eating minimally or not at all, and there is essentially no or minimal administration of fluids, hemodialysis is not required "per schedule" as is generally perceived and executed. With an increasing number of inpatients undergoing hemodialysis or CRRT, the reduction of 1 or 2 dialytic treatments liberates personnel for greater logistical execution, that is, longer therapies where required. In addition, there is the aberrant concept of instituting dialysis to prevent hyperkalemia at serum potassium concentrations mildly exceeding 5 mmol/L. One must always rule out pseudohyperkalemia. There is always the possibility that tourniquet- and fist-clenching–induced hyperkalemia

is present, especially in patients in whom blood has been drawn repeatedly.[19] This explanation is rarely considered, and patients are dialyzed for a venipuncturist's diligence, the consequence of which is removal of potassium precious to the *milieu intracellulaire*. This scenario represents a misfear because the vast majority of patients do not develop electrocardiographic changes of severe hyperkalemia with consequent arrhythmias. Two decades ago, Allon and colleagues[20] delineated the phenomenon of "fasting hyperkalemia" for which the solution is simply sugar, that is, carbohydrate administration, with the foreknowledge that CKD is accompanied by insulin resistance, which may occur at earlier stages of CKD than heretofore appreciated.[21,22] Because glucose and potassium entry into cells represents 2 different pathways, one must fully appreciate that insulin is the hypokalemia-inducing agent, not glucose. Per the collective body of evidence from rubidium studies in ESRD patients, it is probable that total potassium bodily stores are in deficit in a substantial proportion of the hemodialyzed population.[23-25] So, why remove even more potassium, when redisplacement into cells is the correct therapeutic maneuver, and we already know how to do that?

The Bauhaus architect, Ludwig Mies van der Rohe (1886-1969), has been famously miscredited with stating that "less is more." Later, one of his admirers, an industrial designer amplified van der Rohe with "less but better." Nephrologists who work or consult in ICUs should take heed of both these architectural axioms. There will be times that a rational withholding of enthusiasm will provide gains for the critically ill patient.

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## REFERENCES

1. Heung M, Steffick DE, Zivin K, et al. Acute kidney injury recovery pattern and subsequent risk of CKD: an analysis of veterans health administration data. *Am J Kidney Dis.* 2015; http://dx.doi.org/10.1053/j.ajkd.2015.10.019 [Epub ahead of print].
2. Bagshaw SM, Webb SA, Delaney A, et al. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Crit Care.* 2009;13(2):R45.
3. Maynar-Moliner J, Sanchez-Izquierdo-Riera JA, Herrera-Gutierrez M. Renal support in critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359(18):1960-1962.
4. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care.* 2008;12(3):R74.
5. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* 2009;76(4):422-427.
6. Mitchell JP, Schuller D, Calandrino FS, et al. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis.* 1992;145(5):990-998.
7. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359(1):7-20.
8. Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med.* 2009;361(17):1627-1638.
9. Haase M, Bellomo R, Baldwin I, et al. Hemodialysis membrane with a high-molecular-weight cutoff and cytokine levels in sepsis complicated by acute renal failure: a phase 1 randomized trial. *Am J Kidney Dis.* 2007;50(2):296-304.
10. Kidney Disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO Clinical Practice Guideline for acute kidney injury. *Kidney Inter Suppl.* 2012;2:1-138.
11. Alsumrain MH, Jawad SA, Imran NB, et al. Association of hypophosphatemia with failure-to-wean from mechanical ventilation. *Ann Clin Lab Sci.* 2010;40(2):144-148.
12. Ratanarat R, Brendolan A, Volker G, et al. Phosphate kinetics during different dialysis modalities. *Blood Purif.* 2005;23(1):83-90.
13. Ebah LM, Akhtar M, Wilde I, et al. Phosphate enrichment of dialysate for use in standard and extended haemodialysis. *Blood Purif.* 2012;34(1):28-33.
14. Maynar-Moliner JM, Honore PM, Sanchez-Izquierdo JA, et al. Handling continuous renal replacement therapy-related adverse effects in intensive care unit patients: the dialytrauma concept. *Blood Purif.* 2012;34(2):177-185.
15. Honoré PM, Jacobs R, Joannes-Boyau O, et al. Con: dialy- and continuous renal replacement (CRRT) trauma during renal replacement therapy: still under-recognized but on the way to better diagnostic understanding and prevention. *Nephrol Dial Transpl.* 2013;28(11):2723-2728.
16. Lewis SJ, Mueller BA. Antibiotic dosing in critically ill patients receiving CRRT: underdosing is prevalent. *Semin Dial.* 2014;27(5):441-445.
17. Yee J. Newphrologist: the intensive care kidney specialist. *Adv Chronic Kidney Dis.* 2013;20(1):1-3.
18. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med.* 2002;347(25):2010-2019.
19. Don B, Sebastian A, Cheitlen M, Christiansen M, Schambelan M. Pseudohyperkalemia caused by fist clenching during phlebotomy. *N Engl J Med.* 1990;322(18):1290-1292.
20. Allon M, Takeshian A, Shanklin N. Effect of insulin-plus-glucose infusion with or without epinephrine on fasting hyperkalemia. *Kidney Int.* 1993;43(1):212-217.
21. Xu H, Huang X, Arnlöv J, et al. Clinical correlates of insulin sensitivity and its association with mortality among men with CKD stages 3 and 4. *Clin J Am Soc Nephrol.* 2014;9(4):690-697.
22. Leyking S, Fliser D. Insulin resistance in CKD. *Clin J Am Soc Nephrol.* 2014;9(4):638-640.
23. Zannad F, Royer RJ, Issartel G, Robert J. Digoxin in the elderly and in renal failure. Contribution of erythrocyte 86-rubidium uptake tests. *Eur J Cardiol.* 1981;12(5):285-296.
24. Gallieni M, Brancaccio D, Cozzolino M, Sabbioni E. Trace elements in renal failure: are they clinically important? *Nephrol Dial Transpl.* 1996;11(7):1232-1235.
25. Canavese C, DeCostanzi E, Branciforte L, et al. Rubidium deficiency in dialysis patients. *J Nephrol.* 2001;14(3):169-175.