dysfunction results either in podocytopenia and FSGS or in increased proliferative activity and collapsing glomerulopathy and mutations in the nuclear transcription factor WT1 producing DMS (Denys-Drash syndrome) or in FSGS (Frasier syndrome). The specific mechanism by which activation of the Notch signaling pathway in podocytes results in activation of apoptotic stimuli or abnormal differentiation and proliferation still needs elucidation. As suggested by Waters et al., Notch activation may represent a common pathway to podocyte injury. The resulting phenotype and glomerular histopathology may depend on levels of Notch signaling in podocytes or the activation of collateral pathways, which may positively or negatively influence Notch signaling. Notch signaling is also mediated by mitochondria functionality, a known modulator of apoptosis and proliferation. Given the role of Notch during different stages of development, it is reasonable to speculate that various forms of glomerular injury are time dependent. Last, the microenvironment and genetic background should also be considered as potential modulators on the level of Notch signaling, as demonstrated in other organ systems.

On the basis of these recent observations, it would be helpful to investigate the role of Notch signaling in other podocytopathies, because it may represent a common pathway for podocyte injury and a potential candidate for new therapeutic strategies.

DISCLOSURES
None.

REFERENCES


Dialysis Dosage in Acute Kidney Injury: Still a Conundrum?

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In medicine, a key necessity is understanding how to dose therapy to achieve a desired response. For treatment of patients with chronic and acute kidney problems, dialysis techniques are routinely applied; however, establishing a dosage–response relationship for dialysis techniques is challenging both in the chronic and the acute setting. In this issue, Tolwani et al. report the results of a single-center, randomized, controlled trial comparing a high dosage (35 ml/kg per h) with a standard dosage (20 ml/kg per h) of continuous venovenous hemodi–filtration in patients with severe acute kidney injury (AKI). There was no benefit for renal recovery or overall survival with the higher dosage. These results are contrary to three other controlled trials published recently. These studies showed a survival advantage by providing a higher dosage of dialysis, either with a continuous renal replacement therapy dosage ≥35 ml/kg per h or with daily compared with every-other-day intermittent hemodialysis. Only one other study failed to show a survival benefit despite application of higher dosages; however, it was underpowered. Given the varied results of these studies, several important questions emerge. Is dialysis...
“dosage” important in AKI? If so, then is the inability to show benefit solely due to a limited sample size, or is there an alternate explanation? Do we have the right measures of dosage? What should be the ideal target parameter(s)? Is a fixed dosage the right approach given changing parameters in our patients over time? Have other important parameters related to process of care been addressed?

For the trial by Tolwani et al., as for every negative study, two important aspects must be ascertained before concluding that the treatment is not efficient. First, is the power adequate (≥80%)? Second, were the assumptions used for the power calculation realistic? This trial had a power of 80% to detect a 20% difference in survival, if the mortality rate in the standard dosage group was 65%. The observed mortality rate was 56% in the standard-dosage and 49% in the high-dosage arm. The proposed effect size of 20% difference in survival may have been overestimated. Ronco et al.4 used similar effluent volumes (20 versus 35 ml/kg per h) for continuous venovenous hemofiltration and showed a survival difference of 16%. In the trial by Tolwani et al., to detect a 16% difference assuming that other parameters stay unchanged, a total of 300 patients (instead of 200) would have been required. The study would thus be underpowered to detect the smaller effect size, and this is further compounded by the observed lower mortality in the standard-dosage arm (56 versus 65%).

In addition to the low power, other factors may be relevant. The concept of dialysis “dosage” in AKI continues to be a puzzle. Extrapolation of urea kinetic modeling (Kt/V) to critically ill patients with AKI is difficult because of a nonsteady state, leading to a variable increase in urea generation rate, alterations in total body water and its compartmental distribution, and a changing renal excretory capacity that is not easily quantified. Additional challenges are imposed when dosage is considered for different modalities of dialysis that vary in operational characteristics (diffusion, convection, and adsorption), duration (intermittent and continuous), and frequency. Consequently, two broad approaches have emerged for quantifying dosage. In intermittent hemodialysis, the “intensity” of dialysis adjusted by the duration and frequency of dialysis is generally equated with a standard or high dosage.7 Measurements of prescribed and delivered Kt/V are often included as objective measures of adequacy but are subject to variation.8 In contrast, in continuous therapies, the amount of effluent (ultrafiltrate + dialysate) per kilogram of body weight per unit of time is currently proposed as a measure of dialysis dosage.9 This assumption is considered reliable because the effluent is generally completely equilibrated and the sieving coefficient (effluent/plasma concentration) of small solutes is approximately 1. Hence clearance (sieving coefficient × volume) is equivalent to the effluent volume. Alternative methods to quantify dosage independent of the modality and schedule of dialysis account for the generation and time-averaged concentration of urea but have not been widely accepted.10

Given the uncertainty of our approach to dialysis dosage, it is instructive to consider the concept of dosage in another discipline. As an example, for ventilatory support, the “dosage” is tidal volume in ml/kg, whereas the response is respiratory status reflected by arterial oxygen and CO2 levels. What should be the “response variable” for dialysis dosage? Dialysis removes small and middle molecular solutes, adds solutes to correct electrolyte and acid-base abnormalities, and removes fluid. Consequently, response variables should quantify changes in solute concentrations, fluid status, and acid-base and electrolyte control. If we accept these principles, then our current strategy for dialysis dosage may not be adequate. Although the benefit of clearing middle-size molecules in AKI is still controversial, middle molecule removal has not been included in either the dosage or the response in any of the trials to date. Similarly, fluid balance was shown to have an independent effect on outcomes in critically ill patients11 and in patients who had AKI and were treated with continuous renal replacement therapy.12 It is evident that fluid management is an integral component of dialysis dosage yet is not quantified in most studies. In the trial by Tolwani et al.,13 there is no description of the fluid balance status at onset or during the study. In addition, the prescribed fluid removal capacity was limited to a total ultrafiltration amount of 0.7 and 1.25 L in the standard- and high-dosage groups, clearly inferior to the ultrafiltration rate in the study by Ronco et al.4 The mean effluent volume delivered was actually less than prescribed (17 and 29 ml/kg per h in the low- and high-dosage arms), further reducing the convection clearance and the ultrafiltrate available for fluid balance. These factors are not balanced by the randomization process, likely influence the results over time, and could possibly account for differences in outcomes in dosage-outcome trials. Thus, to make ideal comparisons, dosage parameters should probably standardize small and middle molecules and fluid removal capacity, whereas target parameters assessing the adequacy of the dialysis dosage delivered should measure removal of small and middle molecules and fluid. Response to dialysis dosage should ideally encompass time-averaged concentrations for small and middle molecules and acid base, electrolyte, and fluid balance.

Another important concept is the fluctuation in requirements of acute renal replacement therapy over time. In ESRD, the minimal GFR required before initiating dialysis is not precisely known, ranging probably between 5 and 15 ml/min13,14; however, because the kidney is not expected to recover, the initial dialysis prescription needs little adjustment except to compensate for changes in residual renal function. In contrast, in critically ill patients with AKI, dialysis is used to support organ function with the goal that the kidney will recover. Consequently, the dosage of dialysis requires frequent adjustment to meet individual needs.15 Results from previous studies of AKI tended to show the superiority of a dialysis dosage of 35 versus 20 ml/kg per h, which represents a small molecule clearance of 40 versus 23 ml/h in a 70-kg patient.4,5 Thus, in critically ill patients with AKI, the demand for renal support seems higher than that in patients with ESRD.16 In AKI, as the severity of illness and the capacity of kidneys and other organs...
improve, the needs for renal support decrease over time, but to what extent? All studies to date have used a fixed dosage at start; however, dosage adjustments have not been done related to the underlying severity of illness and renal capacity over time. This could lead to under- or overdialysis and contribute to adverse outcomes. We should recognize the changing needs of critically ill patients and be prepared to support them with the appropriate dosage of dialysis delivered by the most effective modality.

In conclusion, we believe that to demonstrate efficacy and effectiveness of a dosage–response relationship, we must standardize our dosage criterion, define target parameters that directly reflect the effect of the dosage, and assess these parameters sequentially. Dosage adjustments to meet the changing needs should be incorporated into the trial strategy, and elements of process of care should be captured to validate the adequacy of the randomization process.16 We anticipate that two large trials (Acute Renal Failure Trial Network [ATN]7 and RENAL9) examining the dialysis dosage–outcome relationships are due to be reported in the next few months. These trials will provide unique opportunities to assess these elements and validate the relevance of dialysis dosage in AKI. In the interim, we should not forget the key attributes of good clinical practice of sequentially evaluating our patients and matching the dialysis prescription to their needs.

ACKNOWLEDGMENTS

Josée Bouchard is a recipient of a research fellowship from the Kidney Foundation of Canada.

DISCLOSURES

None.

REFERENCES


See related article, “Standard versus High-Dose CVVHDF for ICU-Related Acute Renal Failure,” on pages 1233–1238.