OPINION

Effluent volume and dialysis dose in CRRT: time for reappraisal

Etienne Macedo, Rolando Claure-Del Granado and Ravindra L. Mehta

Abstract | The results of several studies assessing dialysis dose have dampened the enthusiasm of clinicians for considering dialysis dose as a modifiable factor influencing outcomes in patients with acute kidney injury. Powerful evidence from two large, multicenter trials indicates that increasing the dialysis dose, measured as hourly effluent volume, has no benefit in continuous renal replacement therapy (CRRT). However, some important operational characteristics that affect delivered dose were not evaluated. Effluent volume does not correspond to the actual delivered dose, as a decline in filter efficacy reduces solute removal during therapy. We believe that providing accurate parameters of delivered dose could improve the delivery of a prescribed dose and refine the assessment of the effect of dose on outcomes in critically ill patients treated with CRRT.

Macedo, E. *et al. Nat. Rev. Nephrol.* **8**, 57–60 (2012); published online 1 November 2011; doi:10.1038/nrneph.2011.172

Introduction

Until recently, dialysis dose was thought to have a pivotal role in improving outcomes in critically ill patients who require continuous renal replacement therapy (CRRT). The relationship between treatment dose and outcome in patients with acute kidney injury was first investigated prospectively in a single-center study in which patients were randomly assigned to postdilution continuous venovenous hemofiltration (CVVH) at 45 ml/kg/h, 35 ml/kg/h or 20 ml/kg/h. Patients receiving a higher dose had better survival than those randomized to 20 ml/kg/h.[1] Subsequently, conflicting results from small randomized clinical trials of both intermittent and continuous modalities of RRT have highlighted the need for larger multicenter trials.[2–5]

Two large multicenter, randomized, controlled clinical trials did not find any benefit of an intensive dialysis dose over a standard dose.[6,7] These trials have dampened the enthusiasm of clinicians for considering dialysis dose as a modifiable factor influencing outcomes. The results have contributed to the perception that increased dialysis dose might not be of benefit in improving outcomes and have also increased the tendency to not assess dialysis dose.[8] Although the evidence of the lack of benefit of increasing the dialysis dose above the levels that were tested in these trials is undeniable, it is instructive to evaluate the assumptions and findings in these studies.

Competing interests
The authors declare no competing interests.

Assessing delivered dose

Following the study by Ronco *et al.*[1] in patients on CVVH, all subsequent studies of CRRT have considered the delivered dose as equivalent to the total effluent volume, expressed as a weight-adjusted hourly effluent rate. This assumption is based on the principle that the operational characteristics of a low ultrafiltration (in patients on CVVH) and dialysate flow (in patients on continuous venovenous hemodialysis [CVVHD] or continuous venovenous hemodiafiltration [CVVHDF]) result in complete saturation of small solutes in the effluent. Consequently, clearance is equal to the total effluent volume, which is calculated as the sum of net fluid removal rate (Qnet), the spent dialysate (Qd) and replacement fluid (Qr) in combined therapies such as CVVHDF, and the sum of Qnet and Qr in CVVH (Box 1). Therefore, effluent volume is perceived to represent clearance in CRRT and has been widely utilized to prescribe and measure the dose in these modalities. A key supposition for this statement is that filter permeability remains constant over time (effluent fluid urea nitrogen [FUN]/blood urea nitrogen [BUN] ratio = 1). Unfortunately, this assumption is not correct.

Three important treatment-related factors could reduce the actual delivered dose in patients receiving CRRT. First, concentration polarization resulting from an increased concentration of rejected solvents on the membrane surface as a function of transmembrane flow, and protein fouling owing to the adsorption or deposition of matter on and in the separation layer of the membrane, lead to a concentrated layer immediately adjacent to the membrane and a decrease in diffusive transport (Figure 1).[9] Both concentration polarization and/or membrane fouling lead to the need for an increased transmembrane pressure in order to maintain an adequate ultrafiltration rate and also lower the concentration of potentially important solutes in the effluent.[10] Second, filter clotting progressively causes a decline in the sieving coefficient of the membrane and reduces filter permeability. The measurement of effluent volume is driven by the settings on the CRRT machine pump and does not reflect changes in filter permeability. Additionally, a third issue presents when predilution is applied. The prefilter infusion of replacement solution reduces the concentration of solutes in the plasma and decreases solute clearance. Brunet *et al.*[11] showed that this decrease in urea clearance could be as high as 15%.

The importance of these three factors is not limited to their effect on the delivered dose of dialysis. Filter clotting, membrane fouling, placement of the replacement solutions and other treatment-related factors can also affect drug clearance. Periodic monitoring of therapeutic drug concentration in the serum and effluent of patients on CRRT would improve drug delivery and maintain its therapeutic efficacy. However, future research is needed in this area to better characterize the effect of technique-specific factors on drug clearance.

The sieving properties of the membrane can be assessed at any given time by measuring the effluent (FUN and BUN).

Box 1 | Assessment of dialysis dose in CRRT

CVVH

- Prescribed dose = (Qr + Qnet)
- Delivered dose = (Qr + Qnet) × S

CVVHDF

- Prescribed dose = (Qr + Qd + Qnet)
- Delivered dose = (Qr + Qd + Qnet) × S

Abbreviations: BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; FUN, effluent fluid urea nitrogen; Qd, dialysate fluid rate; Qnet, net fluid removal rate; Qr, replacement fluid rate; S, FUN/BUN ratio.

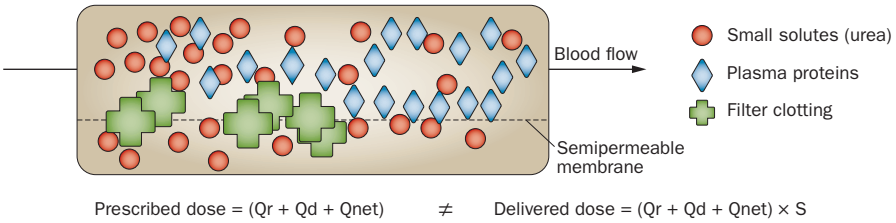

Figure 1 | The effect of concentration polarization and clotting on delivered dialysis dose. Filter efficacy declines over time; protein fouling and filter clotting occur on the membrane and decrease the surface available for diffusion or convection, which reduces the amount of dose being delivered. These important factors must be frequently monitored during continuous renal replacement therapies. Abbreviations: BUN, blood urea nitrogen; FUN, effluent fluid urea nitrogen; Qd, dialysate fluid rate; Qnet, net fluid removal rate; Qr, replacement fluid rate; S, FUN/BUN ratio.

By measuring the FUN/BUN ratio, the solute clearance can be calculated using the formula: effluent volume × FUN/BUN ratio. We have previously shown that the FUN/BUN ratio decreases over time in predilution CVVHDF.[12] The decline in the FUN/BUN ratio is associated with a significant and progressive difference between prescribed clearance (Qnet + Qd + Qr) and delivered clearances of small solutes ([Qnet + Qd + Qr] × FUN/BUN ratio).[12] The difference between prescribed and delivered dialysis dose remained significant after we adjusted for the predilution effect of the replacement fluid using the formula in Box 2.[13]

Dialysis dose in ATN and RENAL

Based on the knowledge that concentration polarization, membrane fouling and filter clotting decrease the FUN/BUN ratio over time, we created a model simulating the influence of the progressive decline in filter efficacy on delivered dose in the Acute Renal Failure Trial Network (ATN)[6] and Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) trials.[7] We hypothesized that the total effluent volume overestimated the actual delivered dialysis dose, as filter function was not taken into account when assessing CRRT dose in these studies. We considered whether changes in delivered dose could have affected the observed difference between the groups receiving intensive and less-intensive RRT in these trials.

Figure 2 shows the expected decline in delivered dose, with a progressive decline in filter efficacy (FUN/BUN ratio). Patients assigned to an intensive dose (35 ml/kg/h in ATN and 40 ml/kg/h in RENAL), and whose filter efficacy declined over time, could have received a dose similar to the upper limit of the less-intensive dose group (20 ml/kg/h in ATN and 25 ml/kg/h in RENAL). For example, in a patient weighing 70 kg, a decline in the FUN/BUN ratio from 1 to 0.9 represents a 10% reduction in the dose in the intensive-dose group; when the FUN/BUN ratio reaches 0.8, there is a reduction of 20% in the delivered dose. For patients in the less-intensive dose group, those in the lower quartile group would receive an inadequate dialysis dose in cases when the FUN/BUN ratio declined to 0.9.

Another consequence of the decline in filter efficacy is the reduction in the difference between delivered dose in the intensive and less-intensive dose arms in each of the studies (Figure 2). The reduction in FUN/BUN ratio progressively decreases the difference in dose received by the intensive and less-intensive dose groups. When the FUN/BUN ratio decreased to around 0.8 in the RENAL and ATN studies, patients in the lower quartile of the intensive-dose group received the same dose as patients in the upper quartile of the less-intensive dose group. This potential overlap of dialysis dose could not be determined in the two trials as solute concentrations in the effluent were not assessed. Compared with routine clinical practice, the monitoring of filters and treatments in the context of these studies was intensified. As a result, filters were changed more often, and the effect of decline in filter efficacy might not have been as pronounced as it is in daily clinical practice. In the ATN trial, more than 77% of the CRRT was performed with a Gambro Prisma® CRRT machine using an AN69 filter. In the RENAL trial, all the filters were AN69. The use of the AN69 membrane in more than 80% of treatments in our study makes our results comparable with those of the ATN and RENAL trials.[12]

In the RENAL trial, the mean filter life was less than 1 day, which was probably related to problems that decrease filter efficacy (anticoagulation was not used in 46% and 51% of the intensive and less-intensive dose groups, respectively). In the ATN trial, information on filter longevity was not provided, but more than 50% of treatments were performed without anticoagulation, which leads to a reduced filter life.[6] The type of anticoagulation used to maintain filter patency could also have an effect on delivered dose. We have shown that, compared with the use of unfractionated heparin, the use of regional citrate anticoagulation significantly increases filter survival time, maintains filter efficacy (increased FUN/BUN ratios) and increases the delivered dose of dialysis.[14] However, even during therapies adequately anticoagulated with citrate, a progressive loss of filter efficacy occurs. In our study, all patients used citrate as a regional anticoagulation.[12] Nevertheless, we could show that 38% of the filters were changed due to filter clotting or concentration polarization. The median duration of filter life was 68.1 h and median FUN/BUN ratios progressively declined over each 12 h period of filter use.[12]

Previous studies of CRRT have shown that delivered dose is 68–89% of prescribed dose.[15,16] In a study by Venkataraman *et al.*,[17] the lower delivered dose of CRRT was caused by interruptions in the CRRT, which led to a total effluent volume over 24 h that was lower than the prescribed dose. In the RENAL trial, the actual effluent volume computed by the machine was used to determine an estimated dialysis dose. The difference between the prescribed dose and this estimated dose was 16% in the high-intensity dose group and 12% in the low-intensity dose group.[7] In the ATN study, the average daily duration of therapy was

Box 2 | Correcting dose for predilution effect

Predilution CVVHDF

- Prescribed dose = (Qr + Qd + Qnet)
- Delivered dose = (Qr + Qd + Qnet) × S

Corrected for predilution*

- Delivered dose = Qnet × ([Qbw/{Qbw + Qr}] + Qd × [Qbw/{Qbw + Qr}]) × S

*The reduction in clearance caused by the use of predilution in CVVHDF can be estimated using this formula.[13] Qbw = (1 – hematocrit) × Qb.
Abbreviations: BUN, blood urea nitrogen; CVVHDF, continuous venovenous hemodiafiltration; FUN, effluent fluid urea nitrogen; Qb, blood flow rate; Qbw, blood–water flow rate; Qd, dialysate fluid rate; Qnet, net fluid removal rate; Qr, replacement fluid rate; S, FUN/BUN ratio.

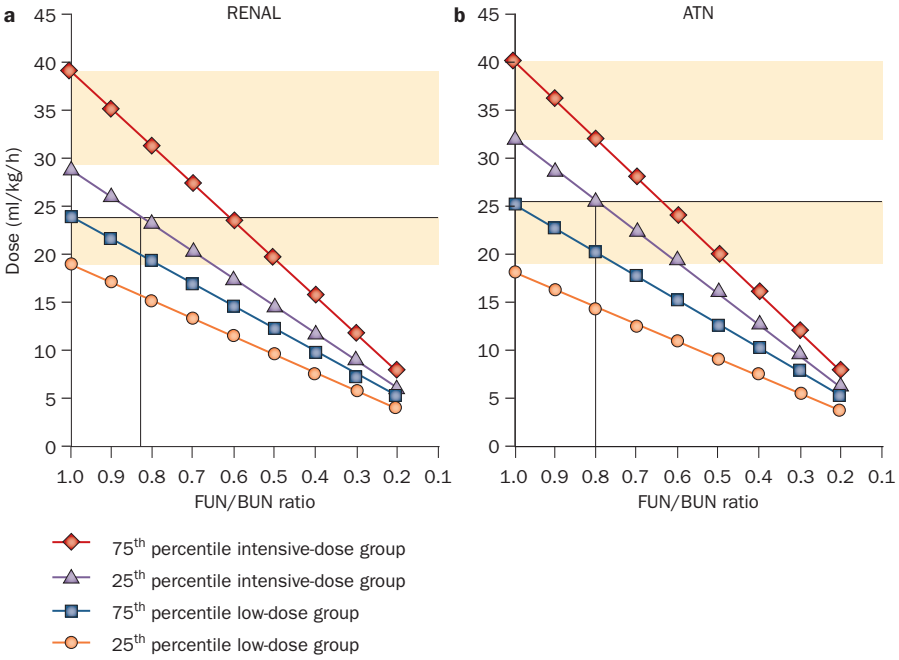

Figure 2 | Decline in delivered dialysis dose as a result of reduced filter efficacy. **a** | RENAL trial and **b** | ATN trial. The decline in filter efficacy is represented by decrements in the FUN/BUN ratio. When the FUN/BUN ratio reaches approximately 0.8, the 25th percentile of the intensive-dose group meets the 75th percentile of the less-intensive dose group. The yellow shaded areas represent the interquartile ranges (data falling between the 25th and 75th percentile) of the intensive and standard doses achieved in the RENAL trial (CVVHDF prescribed effluent volume: standard dose 25 ml/kg/h versus intensive dose 40 ml/kg/h)[7] and the ATN trial (CVVHDF prescribed effluent volume: standard dose 20 ml/kg/h versus intensive dose 35 ml/kg/h).[6] Abbreviations: BUN, blood urea nitrogen; CVVHDF, continuous venovenous hemodiafiltration; FUN, effluent fluid urea nitrogen.

approximately 21 h in both groups, allowing for 89% and 95% of the prescribed effluent volume to be delivered to the intensive and less-intensive dose groups, respectively.[6] As discussed earlier, an additional factor influencing delivered dose is the site of fluid replacement. In the ATN study, in which predilution was used, the combination of blood and replacement fluid flow rates suggest a dose reduction of approximately 15% in the intensive-dose group and approximately 9% in the less-intensive dose group.[8] After correcting for predilution, the mean doses of 35.3 ml/kg/h and 22 ml/kg/h for the intensive and less-intensive dose groups would be approximately 27 ml/kg/h and 19 ml/kg/h, respectively.[8] In our study we showed that correcting for predilution further increased the gap between prescribed and delivered dose.[12] Having no actual FUN/BUN data from the ATN and RENAL trials is a limitation of our simulation model; however, we used FUN/BUN ratios from our previous study to accurately evaluate the real effect of the loss of filter efficacy on delivered dose.[12]

Assessing and delivering dialysis dose in patients with acute kidney injury has become an important issue in the management of critically ill patients. The decline in filter efficacy has significant clinical implications in this context. Based on the results of the ATN and RENAL studies, centers are now more likely to prescribe the minimal dose, 20 ml/kg/h, without implementing any methods to assess delivered dose since the effluent volume is assumed to reflect the delivered dose. However, with the predictable decline in filter efficacy, the gap between prescribed and delivered dose increases the risk of patients receiving inadequate dialysis. Nevertheless, dialysis prescription should not be based solely on small solute clearance. To date, most studies have focused on the clearance of small solutes (that is, urea), but alterations in filter permeability also influence middle molecule clearance. Evidence has shown that fluid balance and the clearance of other solutes (for example, β2 microglobulin) should be considered as part of an integrated approach to quantify and assess the effectiveness of dialysis treatment.[18–20] Future studies should include measured clearances of a spectrum of small and middle molecules to characterize delivered dose.

Conclusions

Considering that delivered dialysis dose is not usually measured and acute RRT is frequently interrupted for various reasons, we recommend increasing the prescribed effluent volume for CRRT by 25% to account for these changes (minimum 30 ml/kg/h). This recommendation is based on previous studies in which the delivered dose of dialysis was lower than the prescribed dose (for example, delivered dose was 82–89% of prescribed dose in the study by Tolwani *et al.*,[5] 79% of the prescribed dose in the Dose Response Multicentre International Collaborative Initiative study[16] and 73–76% of the prescribed dose in our recent study[12]). Thus, if delivered dose is not measured and if filter efficacy is not assessed when prescribing CRRT, we should anticipate these factors and prescribe a dose 25% higher to ensure an appropriate delivered dose. Delivered dose should be monitored by measuring effluent volumes and sieving coefficient (small-solute ultrafiltrate/blood ratio, for example the FUN/BUN ratio) at least daily in patients receiving CRRT. These data should indicate what adjustments of the prescription are needed to enable dynamic adaptation of the dose to meet patient needs. Future modifications of CRRT technology should consider in real-time the measurements of delivered dose of solutes as is done for urea nitrogen in existing hemodialysis systems. We believe that providing more accurate parameters of delivered dose will improve the delivery of dialysis and assessment of the effect of dose on outcomes in critically ill patients treated with CRRT.

*Division of Nephrology, University of São Paulo, Avenida Doutor Enéas de Carvalho Aguiar 255, CEP 05403-000, São Paulo, Brazil (**E. Macedo**). School of Medicine, Universidad del Valle, Casilla 4742, Cochabamba, Bolivia (**R. Claure-Del Granado**). Division of Nephrology, School of Medicine, University of California, 200 West Arbor Drive, San Diego, CA 92103, USA (**R. L. Mehta**).*

Correspondence to: R. L. Mehta
rmehta@ucsd.edu

1. Ronco, C. *et al.* Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* **356**, 26–30 (2000).
2. Schiffl, H., Lang, S. M. & Fischer, R. Daily hemodialysis and the outcome of acute renal failure. *N. Engl. J. Med.* **346**, 305–310 (2002).
3. Bouman, C. S., Oudemans-Van Straaten, H. M., Tijssen, J. G., Zandstra, D. F. & Kesecioglu, J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit. Care Med.* **30**, 2205–2211 (2002).
4. Saudan, P. *et al.* Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int.* **70**, 1312–1317 (2006).
5. Tolwani, A. J. *et al.* Standard versus high-dose CVVHDF for ICU-related acute renal failure. *J. Am. Soc. Nephrol.* **19**, 1233–1238 (2008).
6. Palevsky, P. M. *et al.* Intensity of renal support in critically ill patients with acute kidney injury. *N. Engl. J. Med.* **359**, 7–20 (2008).
7. Bellomo, R. *et al.* Intensity of continuous renal-replacement therapy in critically ill patients. *N. Engl. J. Med.* **361**, 1627–1638 (2009).
8. Ronco, C. *et al.* Dialysis dose in acute kidney injury: no time for therapeutic nihilism—a critical appraisal of the Acute Renal Failure Trial Network study. *Crit. Care* **12**, 308 (2008).
9. Marshall, M. R. Current status of dosing and quantification of acute renal replacement therapy. Part 1: mechanisms and consequences of therapy under-delivery. *Nephrology (Carlton)* **11**, 171–180 (2006).
10. Feldhoff, P., Turnham, T. & Klein, E. Effect of plasma proteins on the sieving spectra of hemofilters. *Artif. Organs* **8**, 186–192 (1984).
11. Brunet, S. *et al.* Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. *Am. J. Kidney Dis.* **34**, 486–492 (1999).
12. Granado, R. C. *et al.* Effluent volume in continuous renal replacement therapy overestimates the delivered dose of dialysis. *Clin. J. Am. Soc. Nephrol.* **6**, 467–475 (2011).
13. Clark, W. R., Turk, J. E., Kraus, M. A. & Gao, D. Dose determinants in continuous renal replacement therapy. *Artif. Organs* **27**, 815–820 (2003).
14. Claure-Del Granado, R. *et al.* Effect of type of anticoagulation on delivered dialysis dose of CRRT [abstract]. *American Society of Nephrology Renal Week* TH-P0422 (2010).
15. Evanson, J. A. *et al.* Prescribed versus delivered dialysis in acute renal failure patients. *Am. J. Kidney Dis.* **32**, 731–738 (1998).
16. Vesconi, S. *et al.* and the DOse REsponse Multicentre International collaborative Initiative (DO-RE-MI Study Group). Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. *Crit. Care* **13**, R57 (2009).
17. Venkataraman, R., Kellum, J. A. & Palevsky, P. Dosing patterns for continuous renal replacement therapy at a large academic medical center in the United States. *J. Crit. Care* **17**, 246–250 (2002).
18. Goldstein, S. L. *et al.* Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* **107**, 1309–1312 (2001).
19. Bouchard, J. *et al.* Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* **76**, 422–427 (2009).
20. Bouchard, J., Macedo, E. & Mehta, R. L. Dosing of renal replacement therapy in acute kidney injury: lessons learned from clinical trials. *Am. J. Kidney Dis.* **55**, 570–579 (2010).

Author contributions

All authors contributed equally to discussion of content for the article, researching data to include in the manuscript and reviewing and editing of the manuscript before submission.