Acute kidney injury is associated with morbidity and mortality rates of more than 50% in critically ill patients, despite the potential for recovery of renal function and many advances in medical management. To manage the care of patients with acute kidney injury, we must optimize their hemodynamic and volume status, correct metabolic abnormalities, provide adequate nutrition, and minimize progression of injury. Dialysis is often required, and critical factors to consider when designing a dialysis strategy for patients with acute kidney injury are determining the extent of dialysis and fluid removal, determining when to start dialysis, and selecting the most appropriate method and dialysis membrane.

The optimal dose of dialysis in patients with acute kidney injury is not known. Higher-than-usual doses have been proposed as beneficial, whether therapy is intermittent, for 3 to 4 hours a day, or continuous; however, a recent study has challenged this view. Intuitively, more dialysis might seem better, given the high catabolic state of patients with acute kidney injury, the limited capacity of the kidney to adapt to altered systemic metabolic disturbances, and the fact that no renal-replacement therapy is as efficient as the native kidneys. But more frequent dialysis might result in more frequent episodes of hypotension, which, in the setting of impaired intrarenal auto-regulation, might further increase renal injury. Intuition is of course no substitute for the results of well-designed and well-conducted clinical trials.

In this issue of the Journal, Palevsky et al. report results from the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (ATN) study (ClinicalTrials.gov number, NCT00076219), which was designed as a definitive multicenter study of the effect of dialysis intensity on patient outcomes. Critically ill patients with acute kidney injury, a clinical course most consistent with acute tubular necrosis, and failure of at least one nonrenal organ or sepsis underwent randomization to receive either intensive or less-intensive therapy. In both study groups, patients could receive intermittent hemodialysis or, if hemodynamically unstable, continuous venovenous hemodiafiltration or sustained low-efficiency dialysis. Each week, the intensive-therapy group received a mean of 5.4 treatments of intermittent hemodialysis or sustained low-efficiency dialysis, with a clearance goal, expressed as $Kt/V_{urea}$ (where K is the urea clearance of the dialyzer, t is the duration of dialysis, and V is the volume of distribution of urea) of 1.2 to 1.4 per treatment, or continuous venovenous hemodiafiltration at a mean of 36.2 ml per kilogram of body weight per hour. Each week, the group receiving less-intensive therapy was given three treatments of intermittent hemodialysis, sustained low-efficiency dialysis, or continuous venovenous hemodiafiltration at a mean of 21.5 ml per kilogram per hour. Baseline serum creatinine in both groups averaged 1.1 mg per deciliter (97 μmol per liter), and no patient had an estimated creatinine clearance at baseline of less than 30 ml per minute per 1.73 m$^2$ of body-surface area.

It is notable that the ATN study allowed patients to transition from one mode of renal replacement therapy to another as long as they stayed within the intensive or less-intensive therapy group, a factor that distinguishes this study from prior studies of dose in dialysis. The patients with hemodynamic instability were treated with continuous therapies, and hemodynamically stable patients with intermittent hemodialysis. The type of continuous method used was dictat-
ed by each study center. Although the intent of the study in allowing patients to be transitioned between dialysis methods was to increase the applicability of the results to clinical practice (since changes in patient hemodynamics frequently necessitate changes in dialysis methods), this feature of the study introduces some concerns. When a patient transitions from one therapy to another, the dialysis dose is unlikely to be equivalent. Furthermore, there could be confounding if the patterns of use of methods differed between the high-intensity and low-intensity groups. For example, there was a small overrepresentation of sustained low-efficiency dialysis in the intensive-therapy group.

The rate of death from any cause by day 60 was 53.6% with intensive therapy and 51.5% with the less-intensive approach. Furthermore, there were no significant differences in in-hospital mortality, duration of renal replacement therapy, recovery of renal function, or nonrenal organ failure. These equivalent outcomes occurred despite the fact that there were more episodes of hypotension, hypophosphatemia, and hypokalemia in the intensive-therapy group.

These results contrast with those of single-center studies of intermittent hemodialysis by Schiffl et al.\textsuperscript{2} and continuous venovenous hemofiltration by Ronco et al.,\textsuperscript{3} both of which reported that more intensive therapies were more beneficial. In the study by Schiffl et al., dialysis in the thrice-weekly group was probably inadequate,\textsuperscript{8} as mean values for time-averaged levels of blood urea nitrogen were 104±18 mg per deciliter (37±6.5 mmol per liter), as compared with the predialysis and postdialysis levels of 70±33 and 25±15 mg per deciliter (25±12 and 9±5 mmol per liter), respectively, in the less-intensive dialysis group in the study by Palevsky et al. Thus, the study by Schiffl et al. might be considered a comparison of adequate versus inadequate dialysis, with adverse consequences in the group receiving inadequate dialysis. In contrast, the study by Palevsky et al. compares two treatment intensities, both of which were adequate. The results of the current study are similar to those from a very small study of 34 patients by Gillum et al.,\textsuperscript{9} which showed no effect with greater doses of intermittent dialysis, and those from studies by Bouman et al.\textsuperscript{10} and Tolwani et al.,\textsuperscript{11} neither of which reported any benefit from the higher doses of continuous therapies.

The continuous therapy provided in the current study, however, is not strictly comparable with that provided by Ronco et al., in that Palevsky et al. used dialysis in addition to hemofiltration, whereas Ronco et al. used continuous venovenous hemofiltration only. Arguing against a detrimental effect from adding dialysis to continuous venovenous hemofiltration is a study by Saudan et al.,\textsuperscript{4} which showed a reduction in mortality when dialysis was added to a continuous venovenous hemofiltration dose of 25 ml per kilogram per hour. Another difference from the study by Ronco et al. is technical; Ronco et al. used postdilution replacement fluids whereas Palevsky et al. used predilution replacement fluids, a practice known to reduce effective clearance by approximately 8 to 14%.

Can we generalize the findings of the ATN study? There was a predominance of male patients, raising the question of the extent to which its results can be generalized to female patients. Furthermore, the findings cannot be applied a priori to the increasing number of patients with acute kidney injury on a baseline of chronic kidney disease, since the ATN study excluded patients with advanced chronic kidney disease.

In summary, we can conclude from the ATN study that increasing intermittent dialysis treatments to five to six times per week is not more beneficial than adhering to the more standard thrice-weekly regimen, if the targeted amount of dialysis is a Kt/V\textsubscript{urea} of 1.2 to 1.4, as defined by the protocol. As the authors point out, this conclusion does not mean that dose does not matter, since the targeted standard dialysis goal was greater than what is often achieved in intermittent hemodialysis. Neither does it mean that higher doses of continuous therapies are not beneficial. Given the results of the ATN study, the renal and intensive care communities must now focus on other strategies to help this population of patients. Current approaches to dialysis are probably inadequate to replace critical functions of the kidney other than regulation of volume and electrolyte and acid–base homeostasis. Still lacking are methods that can down-regulate the inflammatory response, which plays a major role in the pathophysiology of acute kidney injury.\textsuperscript{11} Tissue-engineering approaches have been introduced to create active cell-containing devices that someday might complement or replace the passive membrane systems we currently use.\textsuperscript{12}
In addition, new biomarkers might identify injury in a more timely fashion, permitting earlier intervention that results in a reduction in the mortality of this clinical syndrome. We still have a long way to go in treating acute kidney injury.

Dr. Bonventre reports receiving consulting fees from Roche, Sanofi-Aventis, Merck, and Genzyme, having equity interests in Genzyme, and being a co-inventor on KIM-1 patents (patent numbers 6,664,385 and 7,179,901). Dr. Bonventre is also on the board of directors of AMAG Pharmaceuticals.

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