Editorial

Can We Rely on Blood Urea Nitrogen as a Biomarker to Determine When to Initiate Dialysis?

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The article by Liu *et al.* in this issue of *CJASN* is a product of the very productive five-center collaborative effort to study acute kidney injury: The Program to Improve Care in Acute Kidney Disease (PICARD) (1). The authors conclude that "initiation of dialysis at higher BUN [blood urea nitrogen] concentrations was associated with an increased risk for death." The question of when to initiate dialysis in patients with acute kidney injury (AKI) has been debated for nearly 50 years. Teschan *et al.* (2), in a landmark paper published in 1960, introduced the concept of "prophylactic hemodialysis." The rationale and hypothesis that were put forth by these authors were straightforward: Sepsis is a common complication of uremia and often is fatal. If one postulates that uremia contributes to the propensity to develop sepsis, then prophylactic dialysis, by preventing the uremic syndrome, may prevent many of its lethal sequelae. It is interesting to note, however, that prophylactic treatment in this study was defined prospectively as treatment of patients before the nonprotein nitrogen reached 200% (BUN reached 160 mg/dl). In the Teschan study, dialysis was initiated 2 to 3 d after onset of diagnosis of renal failure. Since that time, a number of reports, many retrospective, have addressed this issue of "early *versus* late" initiation of dialysis, although, as in the Teschan study, many used higher levels of BUN as cutoff levels to define "early" than we would use today.

In the studies of Liu *et al.* and others that address the timing of initiation of dialysis, BUN has been used as the biomarker to define the treatment groups. Urea, discovered in human urine by H.M. Rouelle in 1773, is one of the oldest biomarkers in nephrology. For estimation of renal function, however, urea is suboptimal. The blood urea concentration is affected not only by glomerular filtration but also by production and renal tubular handling, which in turn are affected by protein intake, catabolic state, volume status, upper gastrointestinal bleeding, and pharmacologic therapy such as with corticosteroids. In addition, it long has been concluded that urea is likely not a primary contributor to the uremic state. In 1951 Homer Smith commented that "few if any of the clinical signs and pathologic changes associated with renal insufficiency are due specifically to the accumulation of urea in the body, for urea is one of the least toxic of nitrogenous compounds." (3)

Despite its limitations as a biomarker for estimating renal function, BUN has retained its position among routinely ordered tests from most clinical chemistry laboratories. The report by Liu *et al.* suggests yet another role for this venerable biomarker: As a predictor of 60-d mortality in patients who have AKI and require dialysis. Liu *et al.* studied 243 patients who had severe AKI and were enrolled in PICARD. They found that higher predialysis BUN (which they assumed to be a marker for late initiation of dialysis) was associated with higher 60-d mortality. The hypothesis that was generated from this study is that patient survival may be improved by initiating early dialysis in the setting of severe AKI.

Perhaps its imperfections as a GFR marker make BUN all the more suited as a biomarker to predict mortality: Influenced by a panoply of processes—including glomerular filtration, tubular reabsorption of urea, tissue protein catabolism, and even subclinical gastrointestinal hemorrhage—BUN may derive its prognostic ability by being a reflection of numerous clinically important processes. In this context, it is instructive to consider other clinical conditions in which BUN has been shown to predict mortality even in patients without known AKI. In acute decompensated heart failure, patients with BUN >45 had a 2.3-fold higher multivariable-adjusted risk for death at 6 mo than patients with BUN <19; creatinine was not an independent risk factor (4). Among patients with acute coronary syndromes, those with BUN >25 *versus* <20 had a 3.2-fold higher risk for death at 6 mo, even after controlling for serum creatinine and other clinical and demographic factors (5). BUN also has been used in risk scores or independently to predict short-term mortality from pneumonia (6), transplant-related mortality after allogeneic bone marrow transplant (7), and mortality after esophagectomy (8).

Seen in this light, the finding that BUN was associated with a higher risk for death in PICARD is not altogether surprising. The authors started the title of their study "Timing of Initiation of Dialysis..." and defined "late" according to the predialysis BUN concentration, but an equally and perhaps more appropriate title may have been "Predialysis BUN as a Predictor of Death in Patients Who Have AKI and Are Treated with Dialysis." Did patients with higher BUN truly receive late dialysis, and did patients with lower BUN receive early dialysis? Did all of the patients in fact require dialysis? Or did the two groups differ in other, clinically important ways that had more to do with underlying disease severity or comorbidity than with the nephrologists' timing of dialysis initiation?

The authors carefully addressed some of these issues, which haunt all observational studies that involve treatment comparisons, by the use of propensity scores. The propensity score for an individual in this study was the likelihood of initiation of dialysis at a high BUN on the basis of clinical, demographic, and laboratory variables; a propensity score was generated for each individual in the study and then used as a covariate in the final multivariable model. Importantly, the propensity score approach did not alter the findings of the study, which suggests either that the differences between the two groups did not account for the overall findings or that unobserved or unmeasured differences between the two groups were not captured adequately by this method. In any case, as Liu *et al.* recognize, a correlation between BUN and mortality does not prove causation; and even if it does, early treatment with renal replacement therapy to lower levels of this surprisingly predictive biomarker may not make a difference. Of course, this is why we perform randomized, clinical trials—to test hypotheses that are generated by the accumulated knowledge from basic science and observational studies such as the one by Liu *et al.*

Renal replacement therapy has existed for >60 yr, and the sophistication and availability of the technology have grown significantly in the past decade. The study by Liu *et al.* should challenge nephrologists to test rigorously one of our only proven treatments for AKI. The nephrology community has launched the multicenter Acute Renal Failure Trial Network study to address the issue of dose of renal replacement (9), but the issue of timing of initiation still needs to be tackled. It will be a challenge to determine on what basis to randomly assign critically ill patients with loss of kidney function to early *versus* late initiation of dialysis, particularly because we lack reliable methods to assess glomerular filtration or tubular function in the setting of AKI. Furthermore, it may be more important to know whether tubular injury is present and to what extent. BUN may be too nonspecific for kidney injury—despite its ability to predict mortality—to serve as a sensible parameter by which to randomly assign patients. Clearly, a definitive answer will require a clinical trial in which patients with severe AKI are randomly assigned to receive early or late initiation of renal replacement therapy using objective clinical and laboratory criteria. We would propose, however, that a definitive clinical trial to address this issue cannot be done using our current armamentarium of biomarkers. What variable(s) would we use to define "early" and "late" initiation of renal replacement therapy in a heterogeneous group of patients such as those studied in PICARD? Time from the onset of kidney injury? Urine output? Clinical findings of uremia or volume overload? A fundamental problem with studies that deal with this topic is that there is an intrinsic bias that is difficult to escape even in the context of a randomized trial. The group of patients who are randomly assigned to early dialysis inevitably will include individuals who may never have required dialysis had they been monitored for a longer period of time, because AKI often is reversible; the late dialysis group will include fewer such patients, so it would not be surprising if the early dialysis group had a better outcome than the late dialysis treatment group, even if timing of

dialysis has no effect on outcome. Ideally what is needed is a risk score with high negative and positive predictive values that will identify early in the course of AKI whether dialysis will be required. Patients then could be randomly assigned on the basis of this risk score—which should include clinical, demographic, and biomarker values—to early *versus* late initiation of dialysis. Laboratory values that currently are used to gauge the need for dialysis—such as BUN, pH, and potassium—clearly are not sufficient as early predictive biomarkers of AKI that will require dialysis. Several promising new urinary and blood biomarkers are being evaluated (10) that may individually or as a group help to fill this void.

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References

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