Timing of Initiation of Dialysis in Critically Ill Patients with Acute Kidney Injury

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Among critically ill patients, acute kidney injury (AKI) is a relatively common complication that is associated with an increased risk for death and other complications. To date, no treatment has been developed to prevent or attenuate established AKI. Dialysis often is required, but the optimal timing of initiation of dialysis is unknown. Data from the Program to Improve Care in Acute Renal Disease (PICARD), a multicenter observational study of AKI, were analyzed. Among 243 patients who did not have chronic kidney disease and who required dialysis for severe AKI, we examined the risk for death within 60 d from the diagnosis of AKI by the blood urea nitrogen (BUN) concentration at the start of dialysis (BUN ≤76 mg/dl in the low degree of azotemia group [*n* = 122] *versus* BUN >76 mg/dl in the high degree of azotemia group [*n* = 121]). Standard Kaplan-Meier product limit estimates, proportional hazards (Cox) regression methods, and a propensity score approach were used to account for selection effects. Crude survival rates were slightly lower for patients who started dialysis at higher BUN concentrations, despite a lesser burden of organ system failure. Adjusted for age, hepatic failure, sepsis, thrombocytopenia, and serum creatinine and stratified by site and initial dialysis modality, the relative risk for death that was associated with initiation of dialysis at a higher BUN was 1.85 (95% confidence interval 1.16 to 2.96). Further adjustment for the propensity score did not materially alter the association (relative risk 1.97; 95% confidence interval 1.21 to 3.20). Among critically ill patients with AKI, initiation of dialysis at higher BUN concentrations was associated with an increased risk for death. Although the results could reflect residual confounding by severity of illness, they provide a rationale for prospective testing of alternative dialysis initiation strategies in critically ill patients with severe AKI.

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Despite improvements in critical care and dialysis technology, acute kidney injury (AKI) remains associated with high mortality rates, in the range of 50 to 70% (1–5). Although many studies have described the incidence and outcomes associated with AKI, relatively few studies have focused on the association of dialysis practice patterns and outcomes in large, heterogeneous patient populations. Specifically, few studies in the modern era have examined the association of the timing of initiation of dialysis in AKI with mortality. Case series with historical controls that were conducted in the 1960s and 1970s suggested a survival benefit to the earlier initiation of dialysis (6–9), although the relevance of these studies to current practice is questionable, given the high blood urea nitrogen (BUN) levels by current standards in the case and control groups. More recently, single-center studies that were restricted to AKI after trauma (10) and coronary artery bypass surgery (11,12) also suggested a benefit to dialysis initiation at lower BUN concentrations. However, the application of these findings to the general intensive care unit (ICU) population with AKI is unclear.

The Program to Improve Care in Acute Renal Disease (PICARD) is an observational study from five academic medical centers (University of California San Diego, Cleveland Clinic Foundation, Maine Medical Center, Vanderbilt University, and University of California San Francisco [UCSF]) that aimed to identify demographic, process of care, and clinical factors that were associated with favorable and adverse outcomes after AKI among ICU patients (3). For this study, we focused our inquiry on the subpopulation of patients who had AKI and required dialysis and examined the association of timing of initiation of dialysis with mortality. We hypothesized that the timing of initiation of dialysis would vary among and within sites and that delayed dialysis initiation would be associated with increased mortality rates.

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Materials and Methods

Study Participants

During a 31-mo period (February 1999 to August 2001), all patients who underwent consultation for AKI in the ICU were evaluated by PICARD study personnel for potential study participation. Given the

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large number of ICU beds at Cleveland Clinic Foundation, one in six AKI patients were randomly assigned for possible study inclusion, to avoid single-center overrepresentation. AKI was defined as an increase in serum creatinine ≥0.5 mg/dl and baseline serum creatinine <1.5 mg/dl or an increase in serum creatinine ≥1.0 mg/dl and baseline serum creatinine ≥1.5 mg/dl and <5.0 mg/dl, as described previously (13). Patients with a baseline serum creatinine ≥5.0 mg/dl were not considered for study inclusion.

A detailed description of PICARD inclusion and exclusion criteria, data elements, data collection, and management strategies are described elsewhere (3). Patients who were contacted by study personnel and who signed (or whose proxy signed) informed consent were enrolled in the study cohort. The reason for nonenrollment was determined for patients who did not sign informed consent, although no additional data were collected for privacy considerations (14). The Committees on Human Research at each participating clinical site approved the study protocol and informed consent. The modality and the intensity of dialysis and other co-interventions were determined by the treating physician with no influence from study personnel. A total of 398 (64%) of the 618 enrolled patients received dialysis during their ICU stay. To give patients in our analysis an equal "opportunity" to receive dialysis with a low and high degree of azotemia, we excluded individuals with an estimated GFR (eGFR) of <30 ml/min per 1.73 m^2 at the time of hospital admission, reflecting National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) stage IV chronic kidney disease or significant/evolving AKI.

Determination of Degree of Azotemia

Of the 250 PICARD participants who received dialysis during their ICU stay and were admitted to the hospital with an eGFR >30 ml/min per 1.73 m^2, the BUN on the day of dialysis initiation was available in 243 (97%). The median BUN on the day of dialysis initiation was 76 mg/dl. We considered patients whose BUN was >76 mg/dl (n = 121; mean BUN 114.8 ± 28.5 mg/dl) at dialysis initiation as having started dialysis with a high degree of azotemia and patients whose BUN was ≤76 mg/dl (n = 122; mean BUN 47.4 ± 17.9 mg/dl) as having started dialysis with a relatively low degree of azotemia. We used the median BUN rather than a predetermined absolute value (*e.g.*, 100 mg/dl) to allow for sufficient sample size and to provide reasonably wide separation between the two comparison groups.

Statistical Analyses

Continuous variables were expressed as mean ± SD or median and interquartile range and compared using t test, the Wilcoxon rank sum test, or the Kruskal-Wallis test, where appropriate. Categorical variables were expressed as proportions and compared with the Cochran-Mantel-Haenszel χ^2 test or Fisher exact test. We examined the time to death within 60 d of ICU admission using the Kaplan-Meier product limit estimate and compared survival curves with the log-rank test.

We created a propensity score using dialysis initiation at a high BUN as the dependent variable. Using multiple logistic regression, we considered as candidate variables all demographic, clinical, and laboratory factors that were associated with the timing of dialysis initiation on univariate analysis. We retained all variables with $P < 0.20$ in the propensity score. Discrimination of the propensity score model was assessed using the area under the receiver operating characteristic curve, with higher values indicating better discrimination. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. The Hosmer-Lemeshow test compares model performance (observed *versus* expected) across deciles of risk to test whether the model is biased (*i.e.*, performs differentially at the extremes of risk). An NS value for the Hosmer-Lemeshow χ^2 suggests an absence of such bias.

Cox proportional hazards regression was used to determine the associations of timing of dialysis initiation and other covariates, stratified by site and modality (continuous renal replacement therapy *versus* intermittent hemodialysis). Survival was measured from the first day that the patient met the criteria for AKI. We included as covariates factors that were associated with mortality on the day of dialysis initiation (15). Hazard ratios and 95% confidence intervals (CI) were calculated from model parameter coefficients and SE, respectively. Plots of log (−log [survival rate]) against log (survival time) were performed to establish the validity of the proportionality assumption. We fitted models adjusted for covariates only, the propensity score only, and a combination of covariates plus the propensity score.

Two-tailed $P < 0.05$ were considered significant. Statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Results

Table 1 shows demographic, historical, clinical, and selected laboratory values by the degree of azotemia at dialysis initiation. The median BUN by site ranged from a low of 65 mg/dl at UCSF to a high of 89 mg/dl at Vanderbilt, although the difference in median BUN among the five sites was not statistically significant ($P = 0.14$). Considering our definition of high *versus* low BUN, the rate of dialysis initiation at a high BUN ranged from 36% at UCSF to 59% at Vanderbilt ($P < 0.0001$). There was also considerable within-site variation, with the SD ranging from 46 to 57% of the mean BUN at dialysis initiation.

In general, patients who started dialysis at a higher BUN had fewer failed organ systems. There was no difference in the median urine output or the frequency of oliguria between groups (Table 1). Patients who started dialysis later were more likely to be treated with intermittent hemodialysis than with continuous renal replacement therapy ($P < 0.0001$); this difference persisted after controlling for differences in modality assignment by site.

Independent Predictors of Dialysis Initiation with High BUN

Independent predictors of dialysis initiation with a high BUN included a history of chronic obstructive pulmonary disease (odds ratio [OR] 2.78; 95% CI 1.20 to 6.49) and higher serum creatinine (OR 1.43; 95% CI 1.21 to 1.69 per mg/dl). Tachycardia was associated with a lower likelihood of dialysis initiation at a high BUN (OR 0.89; 95% CI 0.77 to 1.04 per 10 beats/min). Patients with higher plasma bicarbonate concentrations (OR 1.05; 95% CI 0.99 to 1.10 per mmol/L) were more likely to start dialysis with a high BUN, as were patients who did not have a pulmonary artery catheter in place at the time dialysis was initiated (OR 1.59; 95% CI 0.85 to 2.99). The last three variables were included in the propensity score equation on the basis of the more liberal P value criterion ($P < 0.2$) but were not significantly ($P < 0.05$) associated with modality assignment after adjustment for the other variables noted above. Other variables that were associated with BUN at dialysis initiation on univariate screening (including gender and hematologic and liver failure) were considered but removed from the multivariable model on the basis of the $P > 0.2$ criterion. The area under the model's receiver operating characteristic curve was 0.75, indicating good discrimination in determining the timing of initiation of dialysis, and the model was well calibrated (Hosmer-Lemeshow χ^2, $P = 0.17$).

Table 1. Clinical characteristics of patients by timing of dialysis initiation[a]

Factor	Low (BUN ≤ 76 mg/dl; n = 122)	High (BUN > 76 mg/dl; n = 121)	P
Mean age (yr)	54.4	57.7	0.11
% Female	47	30	0.007
Race/ethnicity (%)			0.93
white	74	78	
black	7	7	
Asian	10	7	
Hispanic	7	6	
other	2	2	
% Surgery before/at ICU admission	55	55	0.90
% History of hypertension	48	46	0.84
% History of diabetes	22	26	0.43
% History of COPD	8	24	0.008
% History of heart failure	20	26	0.27
% History of coronary artery disease	26	27	0.85
No. failed organ systems (median [IQR]	4 (3 to 4)	3 (2 to 4)	0.008
% Central nervous system failure	31	20	0.04
% Liver failure	43	33	0.01
% Hematologic failure	35	21	0.01
% Cardiovascular failure	46	44	0.74
% Respiratory failure	83	72	0.04
% Mechanical ventilation	55	62	0.34
% Sepsis or septic shock	37	46	0.14
Mean heart rate (per min)	101	94	0.005
Mean SBP (mmHg)	112	115	0.09
Mean DBP (mmHg)	58	56	0.52
Mean temperature (ºC)	36.9	37.0	0.56
Median urine output (mL)	423	424	0.64
Median total bilirubin (mg/dl)	2.6	3.1	0.26
Mean creatinine (mg/dl)	3.4	4.7	<0.0001
Mean BUN (mg/dl)	47.4	114.9	<0.0001
Mean platelets (1000/mm^3)	130	148	0.22
Mean pH	7.35	7.35	0.96
Mean potassium (mEq/L)	4.5	4.7	0.22
Mean bicarbonate (mEq/L)	20.8	21.5	0.35
Mean leukocyte (1000/mm^3)	14.1	14.7	0.67
Mean hemoglobin (g/dl)	10.3	10.3	0.92
Parenteral or enteral nutrition support (%)	33	65	<0.001
Initial dialysis with CRRT (%)	69	43	<0.001

[a]Variable n = for each parameter; for discrete variables, missing considered absent. BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; DBP, diastolic BP; ICU, intensive care unit; IQR, interquartile range; SBP, systolic BP; CRRT, continuous renal replacement therapy.

Timing of Dialysis Initiation and Mortality

Crude survival rates tended to be slightly lower for patients who initiated dialysis at a higher starting BUN, despite a reduced burden of organ system failure (survival at 14 and 28 d 0.80 and 0.65 for "low" BUN *versus* 0.75 and 0.59 for "high" BUN; log rank $P = 0.09$). Adjusted for age, hepatic failure, sepsis, thrombocytopenia, and serum creatinine and stratified by site and initial dialysis modality, the relative risk (RR) for death associated with dialysis initiation with a higher degree of azotemia was 1.85 (95% CI 1.16 to 2.96). Adjustment for the propensity score alone (RR 2.07; 95% CI 1.30 to 3.29) or for the covariates plus the propensity score (RR 1.97; 95% CI 1.21 to 3.20) did not materially alter the association between higher BUN and mortality.

Discussion

The majority of studies on the timing of initiation of dialysis have been case series with historical controls or retrospective case-control series that were performed at the advent of the dialysis era (Table 2). As a result, the BUN concentrations at the start of dialysis in the "early" treatment group in these previous studies were high by modern standards. For example, in a study by Fischer *et al.* (7), patients in the early dialysis group had a mean BUN of 152 mg/dl, compared with a mean BUN of 231 mg/dl in the historical control group. Kleinknecht *et al.* (8) later reported a larger, single-center, retrospective study with historical controls. Subjects in the historical control group were not initiated on dialysis until the BUN exceeded 163 mg/dl or an electrolyte disturbance arose ($n = 173$); subjects in the early dialysis group ($n = 147$) were initiated on dialysis when the BUN exceeded 93 mg/dl. Overall mortality was lower in this study than in other contemporaneous and subsequent reports; however, mortality was lower in those with earlier initiation of dialysis (29 *versus* 42%; $P < 0.05$). The dose of dialysis also varied in the two groups, with higher

Table 2. Timing of initiation of dialysis and its association with mortality

Study	Reference	Year	No. of Patients	Study Design	Predialysis BUN (mg/dl)		Mortality (%)	
					Early	Late	Early	Late
Parsons *et al.*	(6)	1961	33	Cohort with historical control	120 to 150	200	25	88
Fischer *et al.*	(7)	1966	162	Cohort with historical control	152	231	51	77
Kleinknecht *et al.*[a]	(8)	1972	320	Cohort with historical control	93	164	29	42
Conger[a]	(9)	1975	18	Case-control	50	120	20	64
Gettings *et al.*	(10)	1999	100	Retrospective cohort	42.6	94.5	61	80
Bouman *et al.*	(16)	2002	65	Randomized trial	48	105	31	25

[a]Case patients and control subjects differed with respect to both the timing of initiation of dialysis and the dose of dialysis delivered.

doses of dialysis achieved in the early dialysis group. The improvements observed could have been the result of differences in the degree of azotemia at the time of dialysis initiation or dose of dialysis or to other processes of care that changed over time.

In the modern era, Gettings *et al.* (10) conducted a retrospective study of patients with posttraumatic AKI and stratified patients on the basis of timing of the initiation of dialysis into "low" and "high" degree of azotemia groups using a BUN cutoff of 60 mg/dl. Mortality rates among patients who initiated dialysis at the lower BUN cutoff was 61%, compared with 80% among those who started dialysis with higher BUN levels ($P = 0.04$). In a randomized clinical trial, Bouman *et al.* (16) examined the combined effects of timing of initiation and dose of dialysis on 28-d survival among 106 critically ill patients with oliguric AKI. A large fraction of randomly assigned patients (59%) had developed AKI after coronary artery bypass grafting surgery. Patients were randomly assigned to (*1*) early, high-volume hemofiltration ($n = 35$); (*2*) early, low-volume hemofiltration ($n = 35$); or (3) late, low-volume hemofiltration ($n = 36$). On average, patients who were treated with the early strategies were initiated on dialysis with a mean starting BUN of 48 mg/dl. Patients who were treated with the late initiation strategy had a mean starting BUN of 105 mg/dl. This study showed no difference in survival between the early and late initiation strategies (74 and 69% in early high- and low-volume groups *versus* 75% in late low-volume group). However, survival among study patients was significantly higher than among nonstudy patients who were followed concurrently in the same ICU. Moreover, the authors' power calculation was based on a very large effect estimate (40% absolute), so the study likely was underpowered under more realistic assumptions.

Two additional studies (11,12) examined the timing of initiation of dialysis for AKI after cardiac surgery and demonstrated a benefit to earlier initiation of dialysis. These studies used a definition of AKI to justify the provision of early dialysis of a urine output <100 ml during the first 8 h after bypass surgery regardless of solute clearance. Demirkilic *et al.* (11) studied a total of 61 patients; the overall mortality rate in those who were treated with early dialysis was 24%, compared with 56% in control subjects ($P = 0.016$). Elahi *et al.* (12) reported the results of their analysis of 64 patients with postbypass AKI; the overall mortality rate in those who were treated with early dialysis was 22%, compared with 43% in control subjects ($P < 0.05$). However, the relevance of these data to nonpostoperative patients or to patients with nonoliguric AKI is unclear.

The analyses on dialysis initiation from PICARD extend those from previously published reports by including a large study sample from five geographically and ethnically diverse clinical sites, adjusting for confounding using multivariable analysis and by considering selection effects with propensity scores. The results are consistent with or without adjustment for key covariates as well as the likelihood of being prescribed dialysis with a high or low degree of azotemia.

There are several important limitations to this study. Even with adjustment for confounding and selection effects, patients with higher BUN concentrations at the start of dialysis may be different from other patients in ways for which we could not adjust. We attempted to capture these differences with stratification by site and initial dialysis modality and the consideration of several process-of-care variables (*e.g.*, use or nonuse of pulmonary artery catheter) in the development of the propensity score. Despite our efforts, data on several important exposures were not available. For instance, we collected information on whether patients received any nutrition support before starting dialysis but were unable to capture data on cumulative protein or amino acid intake, which could have influenced the BUN concentration independent of kidney function. We eliminated patients who were admitted with an eGFR of <30 ml/min per 1.73 m^2 to give all patients a relatively equal chance to initiate dialysis at the lower BUN level. To avoid lead time bias, we measured day 60 survival in all patients from the first day that they met criteria for AKI, rather than from the first day of dialysis (15). Those with lower BUN concentrations at dialysis initiation may have had relative volume overload (*i.e.*, a larger volume of distribution of urea), which is associated with increased morbidity in the critically ill (17). Although we could have considered other parameters, such as the serum creatinine or urine output, alone or in combination with BUN, these, too, would have been arbitrary and subject to criticism. Virtually all of the previously published literature in this area has focused on BUN, and in the critical care setting, the BUN drives dialysis practice more so than other laboratory or clinical parameters. Finally, although the study's focus was on the timing of initiation of dialysis, other aspects of dialysis care, including frequency and dose, were not assigned uniformly and may have confounded the results.

Conclusion

In a large observational study of AKI in critically ill patients, we demonstrated an association between dialysis initiation with a

high degree of azotemia and mortality, even after adjustment for key confounders and selection effects. Observational studies such as these can be highly informative but should be regarded as hypothesis generating. Among the many unresolved issues in the management of AKI, determining the optimal timing of initiation of dialysis should be considered a high priority. There are potential safety concerns regarding earlier initiation of dialysis (reviewed in [18]), including increased risk for infection from an indwelling dialysis catheter, hypotension associated with therapy and its consequences (including the potential for delayed renal recovery [19]), and leukocyte activation from contact with dialysis membranes, among others (20). Whether these risks outweigh the potential benefits of earlier initiation of dialysis will require prospective testing. A randomized, clinical trial to compare different timing strategies for dialysis initiation is indicated and should be designed and performed carefully.

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See the related editorial, "Can We Rely on Blood Urea Nitrogen as a Biomarker to Determine When to Initiate Dialysis?" on pages 903–904.