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STATE OF THE ART REVIEW

When is dialysis indicated in acute kidney injury?

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ABSTRACT

The indications for dialysis in patients with acute kidney injury (AKI), as well as the dose and timing of initiation, remain uncertain. Recent data have suggested that early initiation of renal replacement therapy (RRT) may be associated with decreased mortality but not with the recovery of kidney function. A blood urea nitrogen (BUN) level of 75 mg/dL is a useful indicator for dialysis in asymptomatic patients, but one that is based on studies with limitations. Different parameters, including absolute and relative indicators, are needed. Currently, nephrologists should consider the trajectory of disease, and the clinical condition and prognosis of the patient are more important than numerical values in the decision to initiate dialysis.

Keywords: acute kidney injury; renal replacement therapy; early dialysis

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THE NEED FOR DIALYSIS INDICATORS FOR ACUTE KIDNEY INJURY

New models for the treatment of acute kidney injury (AKI)[1] and changes in dialysis methods have resulted in a slow decline in mortality from AKI.[2] However, the prevalence and incidence of the syndrome has risen,[3] especially in intensive care units (ICUs). Dialysis currently offers only limited or partial substitution of the multiple functions of the kidneys, and it is not a sufficient treatment for AKI, which is a syndrome involving multiple organs that results in the failure of many systems.[4] Clinically, AKI rarely presents in isolation but is usually a complication of several diseases.[5] The mortality rate for severe AKI has been known to exceed 50% in ICUs, where sepsis is one of the main causes of associated comorbidity.[4,5] For this reason, several studies have attempted to define the indications and optimal dose for dialysis for AKI and the timing of initiation.

UNCERTAINTIES IN AKI DIALYSIS INDICATORS

Since dialysis techniques were developed in the 1950s, dialysis indicators for AKI have been based on the criteria used for patients with end-stage renal disease (ESRD), such as volume overload resistance to diuretics, refractory hyperkalemia, metabolic acidosis, overt uremia, and progressive azotemia in the absence of specific symptoms.[6] These classical indications are, however, subject to interpretation. Questions include how severe volume overload, hyperkalemia, or metabolic acidosis must be to warrant dialysis? If diuretic therapy is initiated, what dose constitutes diuretic resistance? Should dialysis be indicated in persistent oliguria without signs of uremia, azotemia, or hypervolemia?[7] Another issue is that patients with AKI do not present the adaptive responses characteristic of ESRD,[8] and dialysis initiated in the advanced stages of disease is invariably associated with an irreversible clinical condition. For these reasons, precise indications for when to initiate dialysis in AKI do not exist, and there is wide variation in clinical practice.[6,7] The decision to begin dialysis is influenced by factors with varying influence, such as patient age, associated comorbidities, and severity of disease; the local availability of dialysis; influence of the nephrologist's opinion; and cost.[7]

THE EARLY DIALYSIS MODEL

In 1958, Salisbury[9] questioned the indications for dialysis in AKI and suggested that renal replacement

therapy (RRT) should be initiated before the more advanced stages occurred, in an attempt to reduce patient mortality. Some retrospective and observational studies proposed initiating early dialysis for AKI although this treatment is not fully established. Several years after the initial proposal, a mortality of 33% was observed in patients with oliguric AKI who had started dialysis when their blood nonprotein nitrogen reached 200 mg/dL and obvious uremic symptoms appeared.[10] Although this study lacked a control group, mortality was lower than what had been previously observed.

Other retrospective studies confirmed the usefulness of this new model for early dialysis. A study showed that a survival of 75% in 33 dialysis patients with blood urea nitrogen (BUN) levels of 120–150 mg/dL compared to a survival of 12% in patients who underwent dialysis with their BUN values were higher than 200 mg/dL.[11] Similar results were obtained in another study,[12] in which 162 patients who underwent dialysis when their BUN values were approximately 150 mg/dL had a 43% survival rate, whereas those who started dialysis with BUN values higher than 200 mg/dL had a 26% survival rate. In addition, asymptomatic patients who underwent early dialysis with BUN levels <93 mg/dL had lower mortality (27%) than those who began dialysis with BUN levels >142 mg/dL or exhibited volume overload or electrolytic disorders (42%).[13]

The first prospective study in this area compared 18 patients with posttraumatic AKI who underwent dialysis with BUN <70 mg/dL and serum creatinine <5 mg/dL to patients who did not undergo dialysis until their BUN level approached 150 mg/dL and serum creatinine approached 10 mg/dL, or indications for therapy supervened. The former group showed a mortality of 36%, whereas the latter had a mortality of 80%.[14] Ten years later, a similar study[15] examined patients who submitted to early (BUN <60 mg/dL; creatinine <5 mg/dL) or late dialysis (BUN approximately 150 mg/dL; creatinine approximately 10 mg/dL). Mortality was higher in the second group (59 vs. 47%), but given the small sample size, the difference was not statistically significant. From these studies, the trend became that in the absence of symptoms, early dialysis should be performed with BUN values around 100 mg/dL.

No additional studies examining the timing of RRT initiation for AKI were published until the 1990s. In 1999, Gettings et al.[16] retrospectively studied two groups of patients with posttraumatic AKI submitted to continuous renal replacement therapy (CRRT): 41 patients with BUN <60 mg/dL and 59 patients with BUN >60 mg/dL. They found a higher survival rate in the first group (39 vs. 20.3%; $p = 0.041$). The authors also stratified patients according to BUN levels and showed that the difference in survival levels remained in patients with BUN levels above and below 70 mg/dL (37 vs. 18.4%; $p = 0.035$). A prospective cohort analysis of 306 patients treated with intermittent, high-volume hemofiltration found a mortality of 40%, which was less than predicted by various prognosis indicators. In this study, dialysis in the survivors was initiated at lower BUN levels than in nonsurvivors (73 vs. 78 mg/dL; $p < 0.05$).[17]

In 2004, two similar retrospective studies[18,19] were published in which patients were submitted to CRRT after cardiac surgery. Both studies found that survival rates were higher in patients subjected to dialysis when diuresis levels were lower than 100 mL/8 hr than in patients submitted to dialysis when serum creatinine was higher than 5 mg/dL (77 vs. 45% in the first study, and 78 vs. 57% in the second study; $p < 0.05$). This was independent of BUN and creatinine levels.

EARLY DIALYSIS AND MORTALITY

In a randomized, controlled trial of CRRT, survival rates of 57 and 58% were demonstrated in patients receiving continuous hemofiltration at 35 and 45 mL/hr/kg, whereas among those receiving 20 mL/hr/kg, the survival rate was 41% ($p < 0.05$). In this study, all patients began treatment with BUN values below 60 mg/dL.[20]

Another prospective, randomized trial evaluated CRRT in three groups of patients with oliguric AKI: 35 underwent early, high-volume hemofiltration (72–96 L/24 hr and urea 16 mmol/L); 35 underwent early, low-volume hemofiltration (24–36 L/24 hr and urea 17 mmol/L); and 30 patients underwent late, low-volume hemofiltration (24–36 L/24 hr and urea 37 mmol/L). No difference in mortality (74.3, 68.8, and 75%) was seen between the groups after 28 days, probably because the number of patients in each group was small and the mortality rate was low compared to the patients submitted to hemofiltration in the same ICU who were not included in the study.[21]

More recently, a retrospective study evaluated patients with oliguric AKI and sepsis. In this report, 40 patients who underwent dialysis by conventional indications and BUN 110 mg/dL (historical controls) were compared to a group of 40 patients who submitted to early isovolemic hemofiltration (45 mL/kg/hr) with a mean BUN of 120 mg/dL within 12 hr of ICU admission. Survival was higher in the second group (27.5 vs. 55%; $p < 0.05$). However, because initial BUN values were similar when dialysis was indicated, early indication of RTT could not be concluded.[22]

In 2006, data were analyzed on the timing of dialysis initiation from the Program to Improve Care in Acute

Renal Disease (PICARD), a multicenter observational study. Patients with BUN ≤76 mg/dL (early group) or >76 mg/dL (late group), who were submitted to both intermittent hemodialysis and CRRT, were evaluated. Although there was no statistical difference in mortality between the groups after 14 days (80 and 75%, respectively) and 28 days (65 and 59%), patients from the late group had approximately double the risk of mortality than those in the early group.[23]

An observational study by our group[24] evaluated approximately 350 patients with AKI who underwent different dialysis methods. Those with initial BUN <75 mg/dL had lower mortality (39%) and higher renal function recuperation in survivors (43.5%) than those who underwent dialysis with BUN >75 mg/dL (69.8% mortality and 11.1% renal function recuperation; $p < 0.05$).

Recently, the Acute Renal Failure Trial Network[25] published a multicenter, prospective, randomized, parallel-group trial comparing an intensive-dose strategy and conventional-dose dialysis strategy for AKI treatment. This study showed no significant difference in mortality between patients who received the high dose and those who received the low dose after 60 days. In both groups, dialysis was started with low BUN values of approximately 65 mg/dL.

When the timing of RRT was defined by temporal definitions (days from ICU admission) as conducted by an analysis of data from a large multicenter observational study (BEST Kidney), Bagshaw et al.[26] found that RRT started late (>5 days after ICU admission) was associated with a significantly higher mortality as compared with early RRT (72.8% vs. 58.9%; $p < 0.001$). Late RRT was also associated with an increased duration of RRT and with a longer stay in the hospital. This study showed no significant difference in mortality when the timing of RRF was stratified into "early" and "late" by median urea and creatinine at the time RRT was started.

Recent meta-analysis suggested that the early institution of dialysis might have a beneficial effect on survival but not on the recovery of kidney function in AKI patients.[27] Table 1 summarizes the main studies evaluating the timing of dialysis initiation in AKI patients.

STUDY LIMITATIONS

An approximate BUN level of 75 mg/dL is common for dialysis in asymptomatic patients, although one that is based on studies with limitations. Urea is not an ideal marker, as its generation and volume distribution is highly variable in critically ill patients.

The use of BUN as surrogate for the timing of initiation of RRT is likely to be flawed because it may reflect other situations not related to kidney function such as gastrointestinal hemorrhages and administration of drugs.[28] Many of patients with AKI present with inadequate supply of nutritional substrates, increased concentration of catabolic hormones, and systemic inflammatory response syndrome.[29] Moreover, these patients are often affected by other conditions associated with hypercatabolism as rhabdomyolysis, multiorgan failure, and sepsis syndrome.[29] They experience rapid generation of urea and this scenario can induce early start of dialysis, although it runs as an

TABLE 1. The main studies evaluating initiation of dialysis in patients with acute kidney injury.

Author	Year	Study	*n*	Dialysis	Criteria	Effect
Teschan[10]	1960	R	15	IHD	BUN* < 200	+
Parsons[11]	1961	R	33	IHD	BUN < 120–150	+
Fischer[12]	1966	R	162	IHD	BUN~150	+
Kleinknecht[13]	1972	R	500	IHD	BUN < 93	+
Conger[14]	1975	P	18	IHD	BUN < 70	+
Gillum[15]	1986	R	34	IHD	BUN < 60	–
Gettings[16]	1999	R	100	CRRT	BUN < 60	+
Bouman[21]	2002	P	100	CRRT	6 hr oliguria	–
Demirkiliç[18]	2004	R	61	CRRT	Diu < 100 ml/8 hr	+
Elahi[19]	2004	R	64	CRRT	Diu < 100 ml/8 hr	+
Piccinni[22]	2006	R	40	CRRT	12 hr ICU	+
Liu[23]	2006	O	243	CRRT/IHD	BUN < 76	–

Notes: Study: R, retrospective; P, prospective; O, observational; *n*, number of patients; IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; BUN*, blood nonprotein nitrogen (mg/dL); BUN, blood urea nitrogen (mg/dL); diu, diuresis; Effect (+), improved survival; effect (–), no difference.

indicator of very ill patients, this accumulation does not adequately represent the glomerular filtration rate.[29,30] The approach for protein catabolism quantification offers the advantage to reduce the effect of dietary protein supply on the generation of urea, as estimated by the excess urea appearance rate (urea nitrogen appearance (UNA)).[29] It is also known that assessing the real impact of the levels of urea is too difficult. Liu et al. showed that even with adjustment for confounding effects, patients with higher BUN concentrations at the start of dialysis may be different from other patients in ways for which they could not adjust.[23]

Another factor has become increasingly difficult to use as the measurements to guide initiation of RRT in patients with AKI is the urine output.[27] Problems related to hemodynamic instability present in these patients as well as capillary leak syndromes and decreased plasma oncotic pressure may contribute to increased compartmentalization of body fluids and influence the volume of distribution of urea, often promoting volume overload and predispose to reduced levels of urea.[23,31] Furthermore, nonoliguric AKI as well as the use of diuretic therapy might not afford a meaningful benefit in these clinical settings and instead it might reflect biases toward later initiation of dialysis therapy.[27] Gettings et al., as mentioned before, revealed that the late dialysis group, which had a greater mortality, contained proportionately more nonoliguric patients.[16]

Also, dialysis can be associated with high morbidity and mortality because of risks inherent in the procedure such as bleeding, hypotension, arrhythmia, and infection. Studies suggest that dialysis itself may delay the recovery of renal function because of hypotension or activation of inflammatory cascades by the blood–dialyzer interface.[8,32,33] However, patients subjected to early dialysis tolerate the therapy more easily when clinical conditions are improved.

Recent studies have omitted the progress of patients with AKI who were not subjected to RRT. For a definitive evaluation of the possible beneficial effects of indicators for early dialysis, future studies must be prospective and include all patients with AKI, even those who cannot undergo dialysis. However, without definitive biomarkers for AKI, these studies cannot be performed.[7,34]

CONCLUSION

Some studies have suggested that earlier initiation of dialysis leads to improved survival of AKI patients.[6–9,22–24,32] However, most of these studies are retrospective and use failed methodologies, so definitive conclusions cannot be drawn.

The decision of when to start dialysis in AKI patients is based on several factors. The potential advantages must be balanced against the inherent risks of RRT. Different parameters must be considered, including absolute and relative indications like BUN level, oliguria, and volume overload. More than any numerical values, the nephrologist must consider the trajectory of the disease and the clinical condition and prognosis of the patient.

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