Moving Points in Nephrology

Timing of Initiation and Discontinuation of Renal Replacement Therapy in AKI: Unanswered Key Questions

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Patients with acute kidney injury (AKI) often require initiation of renal replacement therapy (RRT). Currently, there is wide **variation** worldwide on the **indications** for and timing of **initiation** and **discontinuation** of RRT for AKI. Various parameters for metabolic, solute, and fluid control are generally used to guide the initiation and discontinuation of therapy; however, there are currently no standards in this field. Members of the recently established Acute Kidney Injury Network, representing key societies in critical care and nephrology along with additional experts in adult and pediatric AKI, participated in a 3-d conference in Vancouver in September 2006 to evaluate the available literature on this topic and draft consensus recommendations for research studies in this area. Key questions included the following: what are the indications for RRT, when should acute RRT support be initiated, and when should RRT be stopped? This report summarizes the available evidence and describes in detail the key questions, and some of the methods of answering them that will need to be addressed with the goal of standardizing the care of patients with AKI and improving outcomes.

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modes of RRT, and perceived cost of therapy. However, the

specific weight of each of these characteristics on the deci-

sion to start RRT is not fully understood, and strong evi-

A new research network on AKI, the Acute Kidney Injury

Network (AKIN), has been recently established to build con-

sensus terminology and definitions for AKI, to define studies to

validate the proposed terminology and definitions, to explore

feasibility of establishing interdisciplinary collaborative re-

search, and possibly to achieve consensus on current practice

for diagnosis and management of AKI. In this pathway, this

manuscript aims to review current practice and the existing

evidence on indications and timing of application of RRT in

AKI. Furthermore, the present manuscript is the result of a

collaborative AKIN effort to provide interim criteria for the

initiation and discontinuation of RRT in the AKI patient, deter-

mining at the same time an articulated research agenda to

achieve consensus when evidence is missing or insufficient to

make final recommendations for clinical practice.

dence for each point is lacking.

he provision of renal replacement therapy (RRT) in patients with acute kidney injury (AKI) is extremely variable and based primarily on empiricism and local institutional practice and resources (1–3). In particular, there is little consensus on the indications for RRT in general, on the criteria to start RRT, on the appropriate time for initiation or regarding the timing for discontinuation. Criteria to define the need for RRT in AKI have been analyzed by the Acute Dialysis Quality Initiative in previous consensus conferences and publications (1–3)

In general, it appears that the decision to start RRT is affected by strongly held physician beliefs in addition to patient characteristics and logistical or organizational aspects of a given institution. Patient characteristics may include age, severity of illness, and comorbidities (4,5).

These aspects tend to discriminate between absolute and relative indications. Organizational characteristics may include country, type of institution, type of ward, type of physician or healthcare provider, availability of various

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Methodology

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An international multidisciplinary stakeholder committee developed a set of recommendations for current clinical practice and for future research were developed using a modified Delphi approach, as described in an accompanying manuscript (6).

Terminology and Definitions

Before discussing the details of current evidence, interim recommendations, and research agenda, the terminology and definitions for words commonly used (such as indication, timing, and parameters) are as follows:

Indication

The term "indication" refers to a clinical or biochemical condition that defines the need for RRT in the presence of AKI. Furthermore, a specific indication may be absolute or relative. This depends on the fact that each indication can represent a stand-alone condition making RRT mandatory, or it requires concomitant conditions without which RRT can only be suggested or recommended but not considered mandatory. This discussion only deals with RRT for AKI and does not cover the clinical conditions possibly identified as "nonrenal" indications for RRT. Consideration should also be given to a recognition that contraindications to RRT might exist and this may possibly lead to specific conditions in which a "do not dialyze" order should be given. This indeed may describe a situation in which absolute or relative indications for RRT are present but concomitant situations represent relative or absolute contraindications to start and perform the therapy.

Timing

"Timing" refers to the time in which RRT is initiated in patients with AKI. While in the past this issue was mostly described by qualitative criteria (early *versus* late start), there is now consensus that a more quantitative characterization of the timing should be used. For this purpose, timing of RRT start can be described according to the RIFLE classification and/or AKI staging system, according to the number and severity of comorbidities (severity scores) or finally, according to the rate of biochemical changes (trends) or the pace of clinical evolution of the patient (illness trajectory) (5,7,8).

Parameters

Different parameters can be used to indicate the need for RRT. In this setting, it should be considered whether trends or illness trajectories are more significant than absolute values. Parameters are quantitative variables that allow to identify AKI/RIFLE staging (creatinine and/or urine output) or metabolic derangements (blood urea nitrogen [BUN]), degree of fluid overload electrolyte abnormalities, acid-base abnormalities, and, finally, comorbidities and clinical conditions.

What are the indications for RRT in patients with AKI? Practical tables of indications have previously been proposed (9,10). A new approach including additional information is presented in Table 1.

The RIFLE classification is used as this has been extensively

Indication	Characteristics	Absolute/Relative			
Metabolic abnormality	BUN > 76 mg/dl (27 mmol/L)	Relative			
-	BUN > 100 mg/dl (35.7 mmol/L)	Absolute			
	Hyperkalemia $> 6 \text{ mEq/L}$	Relative			
	Hyperkalemia > 6 mEq/L with ECG abnormalities	Absolute			
	Dysnatremia	Relative			
	Hypermagnesemia <mark>> 8</mark> mEq/L (4 mmol/L)	Relative			
	Hypermagnesemia > 8 mEq/L (4 mmol/L)	Absolute			
with anuria and absent deep tendon reflexes					
Acidosis	pH > 7.15	Relative			
	pH < 7.15	Absolute			
	Lactic acidosis related to metformin use	Absolute			
Anuria/ <mark>oliguria</mark>	RIFLE class R	Relative			
	RIFLE class I	Relative			
	RIFLE class F	Relative			
Fluid <mark>overload</mark>	Diuretic sensitive	Relative			
	Diuretic <mark>resistant</mark>	Absolute			

Table 1. The indications for renal replacement therapy in patients with AKI

Practical tables of indications have previously been proposed (9,10). The RIFLE classification has been extensively validated, whereas the AKIN stages still need further confirmation. The data indicate that the indications for and timing of RRT must be viewed within the context of the patient's entire clinical condition, with most indications being relative and a small number of absolute indications. It must also be clearly stated that the traditional indications for timing of RRT in relatively stable patients with isolated acute oliguric renal failure as a single-organ system failure not be applied to critically ill patients with AKI as a component of multiorgan failure. In addition, there is a growing body of evidence that fluid overload as a result of AKI contributes significantly to mortality and morbidity and that control of volume status with CRRT can improve outcomes, especially in pediatric AKI and following cardiac surgery (11–15). A pH cutoff of 7.15 was chosen in parallel to the Surviving Sepsis Campaign guidelines (16). Bicarbonate intervention studies did not show benefit when administered in patients with pH > 7.15.

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Metabolic Abnormalities

Current Practice

This is one of the most widely used indications for the initiation of RRT. Current practice suggests that RRT is indicated if a patient has AKI with an abrupt decrease of glomerular filtration rate and has or is at risk of clinically significant solute imbalance/toxicity or volume overload. RRT is considered the standard of care for such patients.

Current Levels of Evidence for Use of RRT in AKI

The evidence for the benefit of acute RRT is based on the known highly lethal outcome of untreated acute renal failure before the availability of dialysis, early case series, and experience in end-stage renal failure (17,18). However, information on long-term follow-up is limited. RRT improves short-term survival in severe AKI (level III evidence, but unlikely that higher level studies will ever be conducted). There is no consensus on the exact indications for RRT in terms of BUN levels or RIFLE/AKI staging, although there has been a trend in clinical practice toward earlier RRT in the critically ill. Indeed, a small number of studies suggest that earlier initiation is associated with improved AKI outcome in critically ill patients (14,15,19,20).

When should acute extracorporeal renal support be initiated? Although there is general agreement as to the value of RRT in established anuric AKI, there is little agreement regarding time of initiation and there is no accepted definition of what "timing of initiation" means. It may currently be interpreted to mean time from admission to hospital, from admission to ICU, or from time of acute insult. A recent paper introduced the concept of "door-to dialysis time" (21). There is wide variation in clinical practice (19–23).

Three early studies, noted in Table 2, have shown benefit from initiation of dialysis in acute renal failure when BUN is $\leq 100 \text{ mg/dl} (\leq 35.7 \text{ mmol/L}) (24-26).$

Two single-center retrospective studies in patients with AKI following cardiac surgery showed improved survival and shorter hospital stay with earlier initiation of CRRT (14,15). An additional 2 retrospective observational studies have also shown improved outcomes with earlier initiation of RRT (19,20) One of these, a retrospective, cohort study, used a BUN level greater than or less than 60 mg/dl (21.4 mmol/L) as a surrogate of "timing of intervention" (19). In this study from a large trauma center, patients who were started on CRRT at a mean BUN of 42.6 mg/dl (15.2 mmol/L) had a 39% survival compared with a 20% survival in those who started RRT at a mean BUN of 94.5 mg/dl (33.7 mmol/L) (P = 0.041 for mortality difference). In addition, a prospective observational multicenter study of patients with AKI found a significantly higher risk of death in those who had RRT initiated at BUN level greater than 76 mg/dl (27 mmol/L) (20). However, because many factors other than the BUN level at the time of initiation may have resulted in the poorer outcome, this approach is likely to be flawed. The single randomized controlled trial in which the effect of timing on outcome was evaluated in a cohort of critically ill oliguric patients found no beneficial effect of early initiation of RRT. However, the sample size of this study was low (n =106) with three smaller subgroups. Also, late therapy was not as late as in earlier studies. Because of pulmonary edema, nearly half of the patients in the late group started continuous venovenous hemofiltration before serum urea reached 112 mg/dl (40 mmol/L). Moreover, early was not very early because measured creatinine clearance had to be less than 20 ml/min before inclusion (27). Severe hypermagnesemia (>8 mg/dl or >4 mmol/L with absent deep tendon reflexes) is a rare but important indication for RRT in AKI (28-30). Although current knowledge is limited, there is evidence that acute hyperphosphatemia may contribute to AKI and may become an indication for RRT initiation for AKI patients (31).

There are significant differences in the timing of intervention using BUN, creatinine, or urine output with up to two-fold differences in their reported values at the time of initiation of RRT among series (2,9-11).

Table 2. Three early studies showing benefit from initiation of dialysis in acute renal failure when BUN is $\leq 100 \text{ mg/dl}$ ($\leq 35.7 \text{ mmol/L}$)

	Ν	Туре	BUN (mg/dl)	Mortality
Kleinknecht (24)	320	Retrospective	93 versus 164	29% versus 42%
Conger (25)	18	Prospective randomized	50 versus 120	20% versus 64%
Gillum (26)	34	Prospective randomized	60 versus 101	58.8% versus 47.1%

Transition to a Different Modality or Cessation of Treatment

When and how should a course of acute extracorporeal renal support including CRRT be **stopped**? Whereas weaning from mechanical ventilation is a crucial aspect of pulmonary support that has been extensively investigated, it is unfortunate that no such studies exist for renal replacement in general and CRRT in particular. It is likely that appropriate cessation (which includes both when and how) of CRRT is critical to clinical and economic outcomes. No studies have specifically addressed these issues.

The decision to stop a course of treatment or to change modality of treatment is influenced by a variety of factors, including patient characteristics (hemodynamic status, urine output, volume status) and logistic characteristics (staff availability, cost, circuit clotting).

Research Questions

Based on the current state of knowledge, the following research questions were prioritized:

1. Timing of initiation of RRT

What are the indications for RRT in AKI?

What factors determine timing of initiation of RRT?

Does the timing of RRT influence outcome in AKI?

2. Does the timing of discontinuation of RRT in AKI influence renal recovery and patient outcomes?

It was recognized that a large randomized multicenter trial would be required to definitively answer these vitally important questions. However, it was also accepted that such a study would be expensive and unlikely to be funded without first understanding a number other factors related to AKI and subsequent need for RRT. The following question may help to further improve our knowledge: Can we identify different clinical trajectories of AKI, other clinical factors, and biomarkers that are indicative or predictive of subsequent requirement for RRT in patients with AKI?

Proposed Research Methods

It was thought that progress toward answering these questions could be achieved by mining existing databases and by performing a prospective cohort study of patients at risk for AKI, by screening critically ill patients and following their clinical course, AKI stage, Sequential Organ Failure Assessment scores, urinary and blood biomarkers, requirement for RRT, and outcomes.

Once this information is known, it will be possible to develop a focused study protocol and get funding for a large multicenter prospective randomized study of patients with AKI stage III who receive RRT within 24 h of AKI diagnosis *versus* those who receive RRT supported by conventional indications based on the decision of the treating physician.

The suggested criteria for the proposed study are as follows:

Inclusion criteria: patients over 17 yr admitted to ICU with evidence of AKI stage III with intent to continue full life support therapies.

Exclusion criteria: age less than 17 yr, hepatic failure, burns,

cardiac surgery, not fully committed to continuation of ongoing life support therapies.

It is estimated that this would require enrollment of at least 1600 subjects. Regardless of which limb to which patients are enrolled, all would receive RRT to specified KT/V, urea reduction ratio, time averaged urea, or CRRT dose based on ml/kg per hour. RRT in both groups would be discontinued when creatinine clearance exceeds 20 ml/min or based on physician decision. Primary endpoints would include 90 d, 1 yr, and hospital survival and return of renal function. Secondary endpoints would include RRT duration, ICU and hospital length of stay, and functional status on hospital discharge. This study would help to provide clear answers to the critical and unanswered questions around RRT indications and timing of RRT in AKI.

Disclosures

None.

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