SECTION 23

General Principles of Acute Renal Replacement Therapy

CHAPTER 138

Indications for Renal Replacement Therapy in the Critically Ill

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OBJECTIVES

This chapter will:

1. Describe renal indications of renal replacement therapy.
2. Identify nonrenal indications of renal replacement therapy.
3. Discuss the timing of renal replacement therapy in the intensive care unit.

The primary goal of renal replacement therapy (RRT) is to compensate for the abrupt loss of renal function, which characterizes severe acute kidney injury (AKI). Disturbances associated with AKI are volume overload, accumulation of nitrogenous waste products and uremic toxins, hyperkalemia, and metabolic acidosis. In patients admitted to the intensive care unit AKI often is encountered at a very early stage, and thus symptoms may not be as prominent as in community-acquired AKI. Consequently indication to start RRT in critically ill patients frequently is based on very early signs of AKI, such as prolonged oliguria or clinical manifestations of volume overload. Indications to start RRT either aim at replacing failing kidney function (renal indications) or are guided by the intention to clear substances from blood or to provide temperature control (nonrenal indications).

RENAL INDICATIONS

Uremia, Blood Urea Nitrogen, Creatinine

Although the development of overt uremic symptoms such as pericarditis, neuropathy, or coma represents an obvious indication for initiation of RRT, the start of RRT rarely is delayed until the full-blown uremia develops in intensive care units (ICUs). On the other hand, early signs such as anorexia, nausea, vomiting, or changes in mental state are usually nonspecific and hardly may be discriminated from symptoms of other diseases present in critically ill patients. Consequently progressive azotemia frequently is used for indications to start RRT for critically ill patients developing AKI. However, up to now there is no generally accepted threshold for when exactly to start RRT.

The concept of prophylactic hemodialysis in AKI was established by Teschan et al. more than 50 years ago.[1] Based on several retrospective case series between 1950 and 1970 and two prospective trials in the 1970s and 1980s, recommended threshold of blood urea nitrogen (BUN) for initiation of hemodialysis decreased from 165 mg/dL to more than 200 mg/dL to levels ranging from 60 to 100 mg/dL.[2–6] In a retrospective trial investigating timing in CVVH and using a BUN of 60 mg/dL for defining "early" versus "late" initiation of RRT, Gettings et al.[7] found significantly improved survival in the "early" group (average BUN of 43 mg/dL) when compared with the "late" group (average BUN of 94 mg/dL). Another retrospective analysis on 243 ICU patients with AKI from the PICARD (Program to Improve Care in Acute Renal Disease) study used the median BUN of 76 mg/dL for defining early versus late initiation of dialysis. The authors found that the higher degree (>76 mg/dL, mean BUN 114.8 mg/dL) of azotemia at initiation was associated with an increased relative risk of 1.85 for death.[8] However, a more recent single-center study on 302 critically ill patients with AKI demonstrated that urea levels at the time of initiation of RRT do not predict mortality.[9] Overall, BUN or urea levels in the low to median range (i.e., BUN < 110 mg/dL) do not appear to be a valid criterion for starting RRT in critically ill patients.

Creatinine is considered a better indicator of glomerular filtration rate (GFR) and consequently was adopted as a parameter for the definition of AKI in whatever guise. Indeed, serial measurements of creatinine demonstrating relatively small increases is an indicator for increased mortality.[10] Like urea, creatinine is nontoxic, and changes in serum concentration may occur independently of the GFR through changes in volume status, altered production (e.g., in sepsis), reduced muscle mass (e.g., liver cirrhosis), or by drug effects on the

tubular excretion of creatinine.[11] Consequently, although changes in serum creatinine have been suggested for classifying and staging AKI,[10,12,13] the rate or degree of increase in serum creatinine may not reflect adequately the level of decline of GFR[14] and fail to indicate the optimal time point to start AKI.

Volume Overload, Oliguria

Volume overload resulting from salt and water retention is a frequent complication in AKI, occurring in 30% to 70% of the patients in the ICU.[15] Although diuretics frequently are tried for antagonizing oliguria,[16,17] their benefit has not been proven in this situation.[18] Patients with volume overload exhibit greater risk for increased morbidity and mortality. This is supported by the fact that patients responsive to diuretics also show improved outcome, and restrictive fluid management has proven to be beneficial in surgical patients,[19] in ARDS[20] and septic shock.[21] Consequently, in the presence of severe volume overload that does not respond to diuretic therapy, initiation of RRT appears indicated.

Moreover, in the intensive care setting initiation of RRT is guided more frequently by oliguria expected to result in volume overload than by increases in creatinine or BUN.[22,23]

A few retrospective studies investigating early initiation of RRT compared oliguria to conventional criteria (BUN or creatinine) for starting RRT. Two studies investigating patients who underwent cardiac surgery[24,25] started CRRT when urine output was less than 100 mL over 8 hours, a third study[26] in patients with septic shock used oliguria present for more than 12 hours as criterion. All three studies showed significantly reduced hospital or 30-day mortality in patients started on RRT in the presence of oliguria instead of waiting for an increase in BUN or serum creatinine. The only prospective randomized study investigating timing of RRT specifically in patients with diuretic-resistant oliguria could not find a difference between "early" and "late" initiation.[27] However, mortality was low in this study and the sample size very small.

Acute Kidney Injury Stage

The RIFLE (risk, injury, failure, loss of kidney function, and end-stage renal failure) criteria were introduced in an attempt to standardize the definition and staging of AKI.[13] They underwent subsequent modifications by the Acute Kidney Injury Network (AKIN) and finally were framed by the current Kidney Disease: Improving Global Outcomes (KDIGO) and Acute Kidney Injury Network (AKIN) criteria.[10,12] The obvious advantage of these is that they can combine increasing serum creatinine and decreasing urine output rather than considering just one "trigger" in isolation. Several retrospective analyses, mostly using only creatinine for AKI stage determination, showed contradictory results.[22,28–31] In 2015 to 2016 three randomized controlled trials appeared that systematically investigated AKI stages according to KDIGO as indications to start RRT. The German single-center ELAIN trial randomized 231 predominantly cardiac surgical patients with AKI stage II and a serum neutrophil gelatinase-associated lipocalin (NGAL) of more than 150 ng/mL to early versus late RRT.[32] Mortality of patients randomized to early treatment as defined by RRT within 8 hours of AKI stage II had a 35% lower mortality than patients randomized to late RRT (i.e., within 12 hours of reaching AKI stage III). Nearly 90% of the randomized patients received RRT. A multicenter Canadian trial included 100 severely ill patients with AKI stage II and whole-blood NGAL levels of at least 400 ng/mL.[33] Patients were randomized to be either commenced within 12 hours of meeting the inclusion criteria or to be started on RRT when so-called "classic indications" (i.e., hyperkalemia [$K^+ > 6$ mmol/L], acidosis, severe respiratory failure [$paO_2/FiO_2 < 200$]) were reached. There was no difference in mortality between the two groups, but 30% of the patients did not need RRT in the group in which classic indications were applied. The French multicenter AKIKI trial was the largest of these three randomized controlled trials, including 620 mainly medical ICU patients.[34] The "early" treatment group received RRT within 6 hours of reaching AKI stage III, whereas "late" treatment was initiated only when absolute indications were fulfilled, including serum potassium exceeding 6 mmol/L, acidosis, oliguria for more than 72 hours, blood urea nitrogen (BUN) more than 112 mg/dL, or pulmonary edema. Mortality was around 50% with no significant difference between both groups. However, 60% of patients randomized to "late" treatment did not require RRT. Thus, based on current randomized controlled trials (RCTs), a specific AKI stage cannot be recommended for initiation of RRT. It appears that even when using AKI stage III as the only indication, too many patients are receiving RRT who would recover without it.

Electrolyte Disturbances

Hyperkalemia is a common finding in AKI because potassium homeostasis relies mainly on renal excretion. Consequently potassium accumulation does occur frequently in AKI. Additional factors contributing to hyperkalemia are shifts from intracellular space resulting from acidosis, or insulin resistance in critical illness. Sometimes rhabdomyolysis, hemolysis, and adverse effects of certain drugs (angiotensin-converting enzyme [ACE] inhibitors, calcineurin inhibitors, co-trimoxazole, beta blockers) contribute to hyperkalemia. If not treated, hyperkalemia may be rapidly fatal, leading to intractable ventricular arrhythmias or heart failure. Most medical therapies for hyperkalemia provide transitory improvement by shifting potassium into the intracellular space. The only effective measures to decrease whole-body potassium load, however, are diuretic therapy, enteric potassium-binding resins, and RRT. Hemodialysis is the most effective way to remove potassium in renal failure because of the provision of substantially higher potassium clearance (removal of 50 to 80 mmol potassium in a 4-hour session[35]) as compared with continuous forms of RRT. Alternatively, continuous venovenous hemodiafiltration providing sufficient total solute effluent rates should be applicable. Long-term control of potassium may be provided more satisfactorily by continuous forms of RRT. Specific threshold for initiation of RRT in hyperkalemia cannot be recommended generally because it depends on acuity of serum potassium changes and its effect on cardiac rhythm and the patient's overall condition. Usually RRT is not established at serum potassium values below 6 to 6.5 mmol/L.[36]

Both hyper- and hyponatremia do occur in AKI, depending on volume status and remaining water clearance by the kidneys. However, as long as there is residual renal function, it rarely appears necessary to start RRT based on that diagnosis.

Severe hypercalcemia may occur in the setting of hyperparathyroidism or malignancy and can lead to crystal nephropathy, tubular obstruction, and renal failure. In addition to pharmacologic treatment such as bisphosphonates, RRT may be considered as a last-resort treatment for acute derangements of serum calcium with organ

dysfunction.[37] Sustained control of elevated serum calcium levels can be achieved by continuous renal replacement therapy (CRRT) using regional citrate anticoagulation with no or reduced calcium substitution.[38]

Metabolic Acidosis

The kidney is a major player in acid-base regulation. Renal failure results in a continuous increase in organic acids and other unmeasured anions,[39] which occurs because of continuous acid production of around 50 to 100 mEq H^+/d. Furthermore, severe acidosis occurring as a consequence of intoxication with alcohol is an indication for acute HD. These high anion gap acidoses usually are associated with increased osmolar gap (OG = difference between measured and calculated osmolality, normal OG ≤ 10 mosm/L). The role of RRT in other settings of metabolic acidosis, especially lactic acidosis, is not yet answered by clinical studies. However, on the basis of case reports hemodiafiltration and extended hemodialysis may be used to control acidosis in these situations.[40] Although no clear studies do exist that define the exact threshold, an intractable acidosis usually is considered as an indication to start RRT.

NONRENAL INDICATIONS

Sepsis

Severe sepsis and septic shock are associated with AKI in up to 50% of the patients.[41] However, septic patients in the ICU often do not show prominent azotemia when developing AKI. Consequently other criteria such as prolonged oliguria or severe metabolic acidosis may provide sufficient indication to start RRT.[26] Associated with the hypothesis to possibly influence mediators released during sepsis, "prophylactic" RRT has been discussed. The only prospective randomized study investigating this indication could not find any beneficial effect of RRT in severe sepsis without AKI.[42] In fact, an RCT comparing early continuous venovenous hemofiltration (CVVH) versus standard medical treatment in severe sepsis showed that outcome was not improved with CVVH.[43] Furthermore, even by applying high-volume hemofiltration characterized by ultrafiltration rates in excess of 50 mL/kg/hr, neither cytokine levels nor need for vasopressors can be influenced substantially in septic shock.[44] Thus, on the basis of the current evidence, such a procedure cannot be recommended routinely.

Thermoregulation (Hyperthermia, Therapeutic Hypothermia)

The use of an extracorporeal circuit is associated with significant cooling of blood. Although this is considered an unwanted side effect during regular RRT, this property may be used in case of intractable hyperthermia, as occurring in malignant neuroleptic syndrome, malignant hyperthermia, and heat stroke. Case reports of cooling by extracorporeal circuit do exist for all forms of intractable hyperthermia.[45]

Another randomized prospective study reports favorable outcome in patients after cardiopulmonary resuscitation applying either high-volume hemofiltration (HVH) at 37°C or HVH with cooling.[46] In the meantime, several devices are available that allow cooling either externally or by special central venous catheters using a cooled water circuit. Because these devices are easy to use and do not require anticoagulation, RRT for thermoregulation appears to become obsolete.

Drug Overdose, Intoxications

Overdose of drugs or toxins that can be dialyzed is another important indication for RRT in the ICU. Drugs and toxins that can be removed effectively by dialysis are characterized by water solubility, low protein binding, low molecular weight (<500 Da), and small distribution volume. Consequently, RRT may be considered in life-threatening cases of overdosing or intoxication with certain alcohols (e.g., methanol, ethylene glycol),[47] salicylates, lithium, carbamazepine, metformin, valproate, theophylline, or methotrexate (http://www.extrip-workgroup.org). Extended dialysis also has been described as successful in paraquat intoxication, although hemoperfusion appears to be more effective.[48]

Rhabdomyolysis

Rhabdomyolysis occurs in the setting of myocyte necrosis either secondary to traumatic (crush injury, excessive exercise) or nontraumatic injury (ethanol, inherited defects in cellular metabolisms, toxins). This results in release of myoglobin (MW 17 kDa), which may cause AKI by the following mechanisms: vasoconstriction, tubular cell damage by oxidant injury, and tubular obstruction by myoglobin casts. Rhabdomyolysis and myoglobinuria are responsible for about 5% of AKI in the United States.[49] RRT typically is initiated after failure of conservative measures (alkaline-fluid hydration, mannitol, diuretics) to prevent AKI. However, early initiation of RRT for removal of myoglobin in case of excessive rhabdomyolysis accompanied by acidosis and volume depletion, a setting in which AKI must be expected, is recommended by some authors.[50] Because conventional membranes provide insufficient sieving coefficients only for myoglobin (0.4–0.6), usage of super high-flux membranes for CRRT has been described to effectively clear myoglobin.[51,52]

Radiocontrast-Induced Acute Kidney Injury

Radiocontrast nephropathy remains a prominent cause of hospital-acquired AKI associated with significant mortality.[53] A prospective randomized trial investigating the effect of CVVH started before administration of radiocontrast media reported significantly reduced incidence of contrast nephropathy.[54] However, the invasive nature of this procedure and unresolved questions about the pathophysiologic concept of this intervention raises concerns about the utility of this approach in daily practice. Finally, a very recent meta-analysis showed that periprocedural RRT does not decrease the incidence of CI-AKI compared with standard medical therapy.[55]

CONCLUSION

Based on current data there is hardly any evidence-based nonrenal indication for RRT with the exception of drug overdose or intoxication. Renal indications are represented by symptoms of volume overload, severe disturbances of electrolyte or acid-base status, as well as uremia (Table 138.1). However, in critically ill patients severe disturbance of homeostasis may lead to the decision to start before absolute indications become prominent (relative indication). More progressive concepts suggest using the degree of imbalance (or gap) between the patient's metabolic demands (characterized by the severity of disease as well as comorbidities) and

TABLE 138.1

Indications for Renal Replacement Therapy in the Intensive Care Unit

INDICATIONS FOR RRT	ABSOLUTE	RELATIVE
Renal	Uremic signs and symptoms (pericarditis, encephalopathy, pleuritis, etc.) Organ dysfunction resulting from volume overload/ diuretic-resistant oliguria Severe hyperkalemia Severe metabolic acidosis	Progressive azotemia/ rapidly worsening kidney function Progressive volume overload not responsive to diuretics
Nonrenal	Life-threatening intoxications/drug overdose with substances that can be dialyzed	Crush injury/rhabdomyolysis Thermoregulation (hyperthermia) Severe hypercalcemia not responsive to medical treatment

RRT, Renal replacement therapy.

the excretory capacity of the kidney as an indicator to start RRT (Acute Dialysis Quality Initiative XVII).[56]

Key Points

1. Established indications for renal replacement therapy (RRT) in the critically ill are
   - Uremic signs or symptoms
   - Progressive azotemia
   - Volume overload/diuretic-resistant oliguria
   - Electrolyte disturbances, mainly hyperkalemia
   - Metabolic acidosis
2. There are no specific creatinine nor BUN levels that, as a single parameter, indicate the start of RRT.
3. Beside intoxications with drugs that can be dialyzed, there is no relevant nonrenal indication for RRT.
4. There is no evidence of prophylactic RRT in intensive care unit patients.

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