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Acute Renal Replacement Therapies in Critically Ill Patients

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Abstract: Acute kidney injury (AKI) is defined as the abrupt deterioration of renal excretory function, often observed in critically ill patients. The incidence of AKI worldwide ranges between 20 and 200 cases per million population. Sepsis and septic shock contribute to 25-75% of AKI cases. Regardless of the cause, loss of fluid and electrolyte homeostasis and the accumulation of nitrogenous wastes lead to uremia, hyperkalemia, water and sodium retention, and metabolic acidosis. Renal replacement therapies (RRT) aim to mitigate these effects and prevent death associated with kidney failure. There are various modalities of RRT, including intermittent hemodialysis, continuous RRT, as well as different solute elimination techniques. There have been significant advances in membrane technologies and the addition of substances to improve biocompatibility, in addition to new anticoagulation strategies. The aim of this article is to review current RRT alternatives and comment on recommendations regarding their dosage and timing for starting and discontinuing therapy.

Key words: renal replacement therapy; acute kidney injury; hybrid renal replacement therapy

1. Introduction

Acute kidney injury (AKI) is defined as the abrupt deterioration of renal excretory function, manifested by an increase in plasma creatinine and/or reduction or cessation of urine flow in a period of less than 7 days [1]. It may occur due to functional alterations mediated by hemodynamic changes or intrinsic structural damage of the glomeruli, tubules, interstitial or vascular compartment, as a result of exposure to toxins, sepsis or shock [2]. The estimated incidence of AKI worldwide is 20 to 200 per million population. It occurs in 7 to 18% of hospital admissions and 50% of patients admitted to critical care units [3, 4]. Between 25% and 75% of AKI cases are associated with sepsis or septic shock [5]. Regardless of the cause, loss of fluid and electrolyte homeostasis along with accumulation of nitrogenous wastes and other metabolites results in the manifestations of uremia, sodium and water accumulation, hyperkalemia, and metabolic acidosis. The severity of these abnormalities is determined by the magnitude and duration of the initial injury and each patient's own catabolism [6]. The main objective of renal replacement therapies (RRT) is to mitigate the effects of these manifestations and prevent death associated with renal failure.

2. Overview of Renal Replacement Therapy in the Critically Ill Patient

The most commonly used RRT in acute renal failure consists of extracorporeal clearance of the blood of excess water, salt and other solutes through a semipermeable membrane driven by an extraction pump contained in the dialysis machine. Blood collection requires a double lumen central venous catheter connected to the dialysis circuit. The extracted blood is

driven into the interior of a group of hollow fibers, which are composed of cellulose or synthetic polymer semipermeable membranes with an exchange area of 1 to 2.5 m^2, and are compacted into a shell called a blood dialyzer or blood filter. The semipermeable membrane divides the dialyzer into two chambers, one containing the blood inside the hollow fibers, and the other containing dialysate or ultrafiltration fluid. The mechanism of material removal includes transporting water and solutes through membranes through diffusion and convection, as well as adsorbing molecules based on the type of membrane used and the indicated treatment method.

2.1 Vascular access in acute renal replacement therapies

Jugular or femoral catheterization in critically ill patients involves an invasive procedure that may contribute to increased morbidity associated with possible mechanical, infectious or thrombotic complications [7]. A randomized controlled study showed that jugular location of the access does not reduce the risk of infectious complications, except in patients with body mass index (BMI) greater than 28.4 who are at higher risk of colonization of dialysis devices in femoral location [8]. Subclavian catheterization should be avoided because of increased risk of venous stenosis and difficulty of long-term vascular access in case renal function is not restored [9].

2.2 Transport and molecules

Uremic toxins are defined as products of metabolism that are accumulated when renal excretory capacity is impaired. Based on their physicochemical characteristics they are divided into three groups: small soluble molecules (molecular weight < 500 Da), medium soluble molecules (molecular weight between 500-12 000 Da) and protein-bound molecules [10].

The principle of hemodialysis involves the movement of smaller solutes (e.g. urea, creatinine, electrolytes) and water into the dialysate compartment while larger molecules such as blood cells and proteins are retained within the blood compartment. The transport of small molecules occurs from the compartment of higher concentration to the compartment of lower concentration by diffusion mechanism while the transport of plasma water occurs by ultrafiltration as a consequence of the pressure gradient generated on the membrane or convection mechanism [11]. The ultrafiltration rate depends on the porosity of the membrane and the hydrostatic pressure generated by the blood inside the fiber. The transport of medium-sized molecules dissolved in plasma water depends on the ultrafiltration rate and the specific characteristics of the membrane. More than 25 protein-bound uremic toxins divided into phenols, indoles, hippurates, peptides, polyamines and glycosylated products capable of increasing susceptibility to infections and vascular complications have been identified [12]. Due to their binding to plasma proteins, these molecules are removed with hemoperfusion or hemodiafiltration techniques by adsorption mechanisms.

In the past, unmodified cellulose membranes were used in hemodialysis techniques. These are homogeneous and symmetrical membranes with high permeability to small molecules dissolved in plasma water. Synthetic membranes have now been developed with higher water permeability, higher strength, greater size and uniformity in pore distribution and greater asymmetry in their thickness. These changes favor convective transport properties, biocompatibility and stability throughout therapy [13]. Polymers used in manufacturing include polysulfone, polyethersulfone, polyamide, polycarbonate and polyacrylonitrile, among others. Despite these advances, coagulation of the extracorporeal circuit is a frequent complication. The use of anticoagulants makes it possible to maintain the circuit functional; however, it can increase the risk of hemorrhagic complications. The decision to use anticoagulation will depend on the duration of therapy, modality and risks of each patient. Fractionated or unfractionated heparin is the most frequently used pharmacological strategy. More recently, regional anticoagulation with citrate in continuous therapy allows chelation of calcium within the circuit while maintaining stable plasma levels of ionized calcium in the patient [14]. This technique has demonstrated advantages

compared to other methods of anticoagulation. Citrate is considered safer than heparin as it has fewer adverse effects, such as heparin-induced thrombocytopenia, and can reduce the risk of bleeding by avoiding the need for high doses of heparin. It also allows renal replacement therapy to be performed for longer periods of time without interruptions due to filter clotting problems [14]. Importantly, regional anticoagulation with citrate requires careful monitoring of blood calcium and pH levels during the procedure because of the associated risk of metabolic alkalosis. Recent evidence suggests that regional anticoagulation with citrate has immunomodulatory effects, mitigating the inflammatory response by reducing CD11b receptor expression on neutrophils and improving fibrinolysis by reducing plasminogen activator inhibitor type 1 (PAI-1) levels [15]. Some biological components such as heparin and vitamin E have been added to dialysis membranes to increase their biocompatibility. The addition of adsorbent materials such as activated carbon, hydroxyapatite and recently zeolite, allows to improve the clearance of uremic toxins bound to proteins such as p-cresol and medium-sized molecules (e.g. beta-2 microglobulin) [16]. Membranes can be classified according to their water filtration coefficient and their efficiency. Low-flux membranes are those with a filtration coefficient of less than 10 ml/h/mmHg, while high-flux membranes have an ultrafiltration coefficient greater than 20 ml/h/mmHg with a convective clearance of medium-sized molecules greater than 20 ml/min. On the other hand, efficiency is determined by the urea mass transfer coefficient (KoA urea), being less than 500 ml/min in low efficiency membranes and greater than 600 ml/min in those with high transport efficiency.

3. Renal Replacement Therapy Modalities

There are different modalities of renal replacement therapies used in critically ill patients. The evidence is controversial regarding hemodynamic tolerance, survival and recovery of renal function, so the indication should be individualized according to clinical criteria and available resources.

3.1 Classification by time spent on renal replacement therapy

Intermittent hemodialysis is characterized by short periods of permanence (3-6 hours), while continuous renal replacement therapy is indicated for 24 hours and is usually maintained for several days. Regarding mortality, the largest trial performed included 360 patients, most of them with severe hemodynamic compromise. Mortality at day 60 was not different according to technique (32% versus 33%; $p = 0.98$ for intermittent and continuous hemodialysis, respectively) [17]. In contrast, another study involving 166 patients reported higher in-hospital mortality with continuous hemodialysis compared to intermittent hemodialysis (66% versus 48%; $p < 0.02$) [18]. The authors of this study attributed this finding to an imbalance in some characteristics at baseline. A Cochrane systematic review and several meta-analyses concluded a lack of mortality difference between continuous RRT and intermittent hemodialysis [18-21]. Continuous RRT has specific advantages in patients with cerebral edema and elevated intracranial pressure, as seen in acute brain injury or liver failure. Rapid changes in serum osmolality are more likely with intermittent hemodialysis and may precipitate or exacerbate cerebral edema [22]. This is reflected in the recommendation for the preferential use of continuous RRT for these patients in clinical practice guidelines [1-23].

Intermittent hemodialysis is more likely to precipitate intradialytic hypotension in critically ill patients. Dialysis-induced systemic circulatory stress, precipitated by many factors such as intradialytic hypovolemia, hypotension, hypoxia, osmotic changes, vasoplegia, and cardiac arrhythmias, is known to incite and exacerbate cardiac injury and end-organ damage [24, 25]. Clinical detection of dialysis-induced systemic circulatory stress in critically ill patients may be masked by circulatory shock and concomitant multiorgan dysfunction. In a single-center observational study, among critically ill patients receiving continuous renal replacement therapy, 50% experienced intradialytic hypotension after transition to intermittent hemodialysis, with drug requirement being the most potent risk factor [26].

3.2 Classification by solute removal technique

Hemodialysis: The main mechanism of solute removal in hemodialysis is the diffusion of molecules from the blood compartment to the dialysate solution. It is more effective in the removal of small molecules and requires circulation in countercurrent configuration of both compartments to optimize the efficiency of the procedure. It is generally performed with low-flux membranes; however, high-flux dialyzers allow optimizing convective transport during the therapy known as high-flux hemodialysis [27].

Hemofiltration: An exclusively convective therapy in which ultrafiltrate of plasma is obtained through a high-flux membrane in the absence of dialysate fluid. It requires infusion of a sterile solution into the blood compartment to partially or totally replace the reduced plasma volume and decrease the solute concentration. This replacement solution can be administered before the blood enters the hemofilter, with a consequent decrease in the efficiency of solute clearance, or at the exit of the blood path through the hemofilter, increasing the risk of coagulation inside the fibers due to hemoconcentration [28]. High-volume hemofiltration, defined by replacement doses of 50-70 ml/kg/hour of continuous administration or 100 ml/kg/hour for 4-6 hours [29] has been used as a supportive strategy in patients with septic shock by removal of inflammatory response mediators by convective method. Randomized studies have shown variable results regarding the improvement of hemodynamic parameters and survival [30, 31].

Hemodiafiltration: Consists of a combined hemodialysis and hemofiltration technique in which solute removal occurs by diffusion and convection mechanisms. It requires the use of high-flux membranes, the administration of substitution fluid and liquid in the dialysate or effluent compartment [32].

Hemoperfusion: In the hemoperfusion or plasma perfusion technique, blood circulates through a membrane containing specific sorbents, allowing the removal of protein-bound substances, or fat-soluble substances such as uremic toxins, or poisons by adsorption mechanism. Natural sorbents such as activated carbon or zeolite or synthetic sorbents may be incorporated into the membrane pore structure or may be in the form of granules, powder or pellets with extremely high exposure surfaces ranging from 300 to 1200 m^2/g [33, 34].

There are devices designed for hemoperfusion and adsorption of cytokines and endotoxins, with or without associated hemodialysis or hemofiltration. Nonporous carbon and graphene nanoparticles embedded in cryogel efficiently remove cytokines from the bloodstream [35]. More recently, specific adsorption columns have been developed such as CytoSorb®, composed of biocompatible polystyrene divinylbenzene copolymer beads capable of adsorbing medium molecular weight molecules using a combination of size exclusion (60 kDa) and hydrophobic interactions over a total surface area greater than 45,000 m^2, removing inflammatory cytokines (IL-1B, IL-6, IL-8, IL-10, TNF-α, IFN-γ), proteins (myoglobin, ferritin, free hemoglobin), DAMPs (injury-associated molecular patterns) and PAMPs (pathogenic microorganism-associated molecular patterns) that may contribute to dysregulation of the inflammatory response [36, 37]. A multicenter and prospective study of 45 patients with septic shock showed a significant decrease in demand for vasoactive drugs (norepinephrine (51.4%), epinephrine (69.4%), and vasopressin (13%)), a decrease in IL-6 levels (53%), and a decrease in the predicted mortality rate of Apache II from 56.5% to 48.8%, with a focus on starting blood perfusion within the first 24 hours of shock progression [38]. On the other hand, an increase in endotoxin levels was observed in patients with sepsis and LRA. In these patients, specific columns coated with polymyxin B membranes showed a reduced risk of mortality, decreased demand for vasoactive drugs, decreased SOFA (Sequential Organ Failure Assessment) scores, and increased days of non-invasive mechanical ventilation [38]. Oxiris is a dialysis membrane composed of AN69 (polyacrylonitrile) coated with polyethylene amine and heparin. It can adsorb cytokines and endotoxins, and has convective purification function for molecules up to 40kDa through blood filtration. An uncontrolled study showed that after 48 hours of treatment,

the sofa score decreased by 37% [39].

4. Indications and Timing of Initiation of Renal Replacement Therapy

Multiple factors should be considered in the decision to initiate acute RRT in critically ill patients. Observational data show a strong correlation between the magnitude of fluid accumulation and mortality in patients with AKI. This association does not establish causality since patients with greater hemodynamic compromise and risk of death require a greater amount of fluids in the resuscitation phase. The severity of pulmonary congestion and response to diuretics should be considered as criteria for initiating renal replacement in critically ill patients. A randomized controlled study showed that post-surgical patients with refractory volume overload and pulmonary edema benefit from early initiation of RRT with a reduction in 90-day mortality to 39.3% compared to 54.7% in patients starting treatment late [40].

Severe hyperkalemia, defined by myocardial conduction effects or refractory to medical management, is an indication for initiation of RRT in patients with AKI. Metabolic acidosis refractory to bicarbonate infusion or metabolic acidosis secondary to metformin intoxication is indication for initiation of RRT in patients with acute renal failure. Persistent renal failure for more than 72 hours with absolute urea nitrogen values above 112 mg/dl [41], oliguria, or complications from uremia such as encephalopathy, hemorrhage, or pericarditis are indications for immediate initiation of RRT. Preventive initiation strategies before the onset of complications have not shown benefit in short-term survival [42].

5. Renal Replacement Therapy Dosage

The quantification of treatment intensity or dose varies according to the type of RRT indicated. In intermittent hemodialysis, the most frequently indicated dose is 3 to 5 times per week with urea KT/V of 1.2 per session, where KT/V represents the rate or clearance of urea removal during the indicated therapy time normalized by the patient's volume of distribution. On the other hand, a flow rate of 20 to 25/ml/kg effluent is the recommended dose in continuous RRT [1].

Multiple studies have evaluated influence of treatment doses in patients with AKI and RRT. In case of continuous RRT, no differences are demonstrated when comparing effluent doses of 20 and 35 ml/kg/h with similar 60-day mortality of 53.6 and 51.5%, respectively [43]. When comparing effluent doses of 25 ml/kg/h with respect to 40 ml/kg/h in critical patients with indication for continuous venovenous hemodiafiltration, a mortality of 44.7% at 90 days was observed in both groups [44]. The doses, flows and nomenclature used vary based on modality of therapy indicated (Table 1, Table 2).

Table 1. Nomenclature commonly used in indication of RRT

Flow	Symbol	Unit of measure	Meaning
Blood flow	Qb	ml/min	Depends on the indicated therapy modality and vascular access.
Substitution flow	Qs (Qs prefilter/Qs postfilter)	ml/h	Sterile replacement fluid in prefilter or post-filter replacement mode or both in hemofiltration.
Dialysate flow	Qd	ml/min (intermittent hemodialysis) or ml/h (continuous hemodialysis)	Circulating dialysis fluid in dialysis compartment in intermittent hemodialysis or continuous venovenous hemodialysis.
Ultrafiltration	Quf	ml/h	Total volume of fluid removed by positive PTM (transmembrane pressure) per unit of time. Quf = Qs + Quf net
Effluent	Qef	ml/h	Total volume of fluid removed per unit time from the dialysate compartment in hemodiafiltration. Qef = Qs + Qd + Quf net

Net ultrafiltration	Quf net	ml/h	Net programmed fluid loss per unit time. Depends on therapy modality and hemodynamic stability of the patient.

Table 2. Solute clearance in continuous renal replacement therapy (RRT)

Type of therapy	Solute transport	Qs ml/h	Qb ml/min	Quf ml/h	Qd ml/h
Continuous veno-venous hemofiltration	convection	si	150-300	1000-4000	0
Continuous veno-venous hemodialysis	diffusion	no	150-300	0-350	1000-4000
Continuous veno-venous hemodiafiltration	convection and diffusion	si	150-300	(Quf net)	1000-4000

6. Recovery of Function and Cessation of Renal Replacement Therapy

In clinical practice, some simple criteria such as recovery of diuresis or spontaneous decrease in urea nitrogen and creatinine are used as indicators of recovery of renal function and withdrawal of RRT. There are no prospective randomized studies that evaluate precise criteria for the cessation of continuous or intermittent RRT and the decision is usually guided by the characteristics and evolution of each patient, hemodynamic stability, fluid overload, hydroelectrolyte disorders and urinary output. Epidemiologically, the most frequent reasons for cessation of acute RRT are increased urine flow (74%), normalization of pH (70%), adequacy of water balance goals (54%), and normalization of urea nitrogen or creatinine (39%) [45]. Multivariate analyses have shown that urine flows greater than 436 ml/day without diuretics and greater than 2330 ml/day with diuretics 24 hours before RRT withdrawal have the highest sensitivity, specificity (80.9% and 87.9%, respectively) and positive predictive value for cessation of therapy without the need for dialysis readmission [46]. On the other hand, independent risk factors for requiring RRT within 30 days after discontinuation of initial therapy are a high SOFA score, oliguria less than 100 ml/day, pre-existing chronic kidney disease, and age older than 65 years [47]. A retrospective study demonstrated that a 2-hour creatinine clearance greater than 23 ml/min measured 12 hours prior to discontinuing continuous RRT has a positive predictive value of 88.8% odds of not requiring RRT in the next 7 days and was superior to the prediction estimated by urinary flow [48]. Measurement of 6-hour creatinine clearance greater than 22 ml/min has shown a high predictive value of not requiring renal replacement in the next 30 days [43].

7. Conclusion

AKI is an entity of high incidence in critical care units and represents a challenge from its pathophysiology to the therapeutic decision-making process. Volume overload is a frequent complication that compromises the hemodynamic and respiratory status of the critically ill patient, resulting in increased morbidity and mortality. Several investigators have proposed to anticipate these factors, suggesting early indication of RRT, but have failed to demonstrate any mortality benefit except in postoperative critically ill patients.

Likewise, the tendency over the last decades to increase the dialysis dose has not been beneficial either. Citrate anticoagulation is consolidating as the technique of choice when optimizing circuit permeability, reducing the risks of bleeding and thrombocytopenia associated with the use of classic heparin. Finally, the modality of initiation, sequential use of techniques and discontinuation of renal replacement therapy depends on individual clinical criteria and more evidence is required for the development of more specific recommendations.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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