Introduction

The clinical syndromes known as sepsis and septic shock are frequent causes of morbidity and mortality in intensive care units. Acute kidney injury (AKI) according to the RIFLE criteria (risk, injury, failure, loss, end-stage kidney disease) and the AKIN (Acute Kidney Injury Network) is a complication of sepsis and, along with it, increases mortality. Frequently, extracorporeal purification methods need to be instituted along with patient support. During sepsis, acute renal failure is an independent risk factor for mortality as the complexity of the disease increases and the cost of patient care. Renal replacement therapy, in its broadest interpretation, refers to techniques capable of recovering and maintaining homeostasis of the organs during AKI in critical patients. In accordance with this concept, renal replacement could be applied to critically ill patients; however, there is no general consensus about the time, dose or indications. Therefore, use of these techniques is mainly based on the experience of the physicians and available resources.

Definition of AKI

In recent years, the clinical spectrum of AKI has undergone remarkable changes, mainly the emerging concept that AKI is more than a disease of a single organ because it is frequently part of the dysfunction of many diseases.

Acute renal failure is the preferred nomenclature used for the spectrum of renal disease, from a minimal elevation of serum creatinine (sCr), up to renal insufficiency that requires renal replacement therapy. There are >200 deaths due to acute renal failure and, for this reason, a unified definition is needed, not only for standardizing diagnosis and monitoring the progress of the renal insufficiency, but also to standardize the scientific literature. In the year 2004, a group of expert intensivists and nephrologists proposed the consensus of the definition of AKI in the final stage (RIFLE) (Table 1) for acute renal failure. RIFLE was designed to establish the presence of the disease and diagnose it severity. Subsequently, the AKIN modified this definition (Table 2). In this new classification, the categories of risk, injury and insufficiency were replaced by stages 1, 2 and 3, and the classes of renal diseases in the final stage were eliminated. Also, an absolute increase in sCr of 0.3 mg/dL was added to stage 1. Patients who begin renal replacement therapy are considered to be directly in stage 3 (Table 2). However, this classification only partially improved the limitations of the former.

Indications for Renal Replacement Therapy During AKI

Replacement therapy is indicated when a clinical or biochemical condition requires that AKI be corrected. There is no standard definition for the acute renal failure that requires replacement therapy. The decision to initiate it should be based on the judgment of the physician, the organization and available resources; thus, renal replacement therapy is not unique or homogeneous and its indication, time and doses of dialysis will broadly affect its efficacy and safety.

Traditionally, renal replacement therapy has been indicated to purify blood from urea and other uremic toxins along with regulation of the extracellular volume and of the electrolytes. This simple indication has been applied to clinical situations in which the kidney is only a related organ and renal replacement therapy plays an important role in the restoration of homeostasis. Traditional indications
such as metabolic abnormalities, acidosis, oligo-anuria and volume overload are not sufficient to propose renal replacement therapy. Complete clinical evaluation of the patient is required. An indication is absolute when renal replacement therapy is mandatory to treat the situation and relative when the indication depends on the concomitant conditions without which renal replacement therapy is only suggested (Table 1). At present, only a small number of indications are absolute. Most indications are relative and should be taken into consideration in the context of the complete clinical condition of the patient. The absolute clinical indications for renal replacement therapy are symptomatic urea poisoning, decrease in pH < 7.15, electrolyte abnormality with electrocardiogram changes and volume overload and resistance to diuretics. Specifically, volume overload as a result of AKI contributes significantly to morbidity and mortality. Thus, volume control through renal replacement therapy could improve the clinical progression of the patient, especially in children and after cardiac surgery. However, when AKI is part of multiple organ failure (such as in the case of seriously ill patients), the traditional indication cannot be applied in order to decide whether to initiate renal replacement therapy. In this population there is no agreement related with the time of renal replacement therapy.

When Renal Replacement Therapy Is Indicated

Renal replacement therapy is indicated when the nephrologists initiate treatment in a patient with AKI. The decision affects the control of uremia, acidemia, electrolyte imbalance, extracellular volume, expansion and attenuation of inflammation in such a way that it exerts an important influence on patient survival. However, this depends in large part to the definition of time of evolution. Studies in nephrology\textsuperscript{3,4} analyzed the repercussions of time in the evolution of renal replacement therapy using three different definitions. Early and late renal replacement therapy was defined according to arbitrary values based on the average of the BUN and creatinine on admission to the ICU for initiating renal replacement therapy and classified into early, delayed and late. Variable responses were found with respect to improvement with renal replacement therapy when

| Table 1. RIFLE criteria (risk, injury, failure, loss, end-stage renal disease) for AKI |
|---------------------------------|---------------------------------|
| Creatinine criteria/glomerular renal filtration | Criteria of urinary elimination |
| **Risk** | Decrease of renal glomerular filtration > 25% or increase of serum creatinine × 1.5 | UE < 0.5 mg/kg/h × 6 h |
| **Injury** | Renal glomerular filtration > 50% or increase in serum creatinine × 2 | UE < 0.5 mg/kg/h × 12 h |
| **Failure** | Decrease of GFR > 75% or increase in serum creatinine × 3 or > 4 mg% (with acute increase of creatinine > 0.5 mg/dL) | UE < 0.5 mg/kg/h × 24 h or anuria × 12 h |
| **Loss** | Irreversible or AKI persisting for > 4 weeks | |
| **ESRD** | ESRD > 3 months | |

AKI, acute kidney injury; GFR, glomerular filtration rate; ESRD, end-stage renal disease; UE, urinary elimination.

| Table 2. Criteria for AKI |
|--------------------------|--------------------------|
| **Criteria for creatinine** | **Criteria of urinary elimination** |
| **Stage 1** | Creatinine increase × 1.5 or ≥ 0.3 mg/dL | UO < 0.5 mL/kg/h × 6 h |
| **Stage 2** | Creatinine increase × 2 | UO < 0.5 mL/kg/h × 12 h |
| **Stage 3** | Creatinine increase × 3 or creatinine ≥ 4 mg/dL (with acute elevation ≥ 0.5 mg/dL) | UO < 0.3 mL/kg/h × 24 h or anuria × 12 h |

Patients who require renal replacement therapy are considered as stage 3, independently of the stage in which initiation of renal replacement therapy is found.

AKI, acute kidney injury; UE, urinary elimination.
the time was defined by arbitrary values of serum biomarkers compared with the time definition. Hospital mortality was sensitive to the time definition because it increased with renal replacement therapy when the time definition was used and was low or null when the values of creatinine and BUN, respectively, were used. However, when other relevant improvements were evaluated such as duration of renal replacement therapy, hospital stay and dependence on renal replacement therapy upon discharge, renal replacement therapy was associated with greater advantages for all, except the time definition. A more quantitative approximation is required, taking into consideration the inadequacy of the traditional approximation based on arbitrary thresholds of standard parameters. For this purpose renal replacement therapy should be described by referring to the RIFLE/AKIN stage (Tables 1 and 2) and according to the severity of the comorbidity. Even more so, the standard parameters should not be considered as absolute values but as a function of the disease progression.

Dose of Renal Replacement Therapy

In addition to the concept of time, the correct dose prescribed to the patient should be defined. The exact knowledge of the dose is fundamental to provide an effective and safe treatment. The concept of dose of dialysis is well defined in end-stage renal disease in the Kidney Dialysis Outcome Quality Initiative (KDOQI 2006) and, according to general consensus, what is recommended to increase improvement is Kt/V ≥1.2 three times per week. However, the concept of AKI is still not well defined. The dose of delivery of renal replacement therapy is briefly described according to intensity, frequency and clinical efficacy. The efficacy depends on the instantaneous elimination of potassium (K) of a solute and is the volume of blood eliminated from a solute in a determined time. Potassium should not be used for comparing the efficacy of treatments because measurement of the instantaneous elimination does not reflect the total dose released. As a consequence, potassium is higher on intermittent hemodialysis (IHD), which on renal replacement therapy continues, but the volume removed will have the opposite tendency due to the time of application of potassium being longer.

The intensity is the product of the elimination by time (Kt = ml/min × 24 h or L/h × 4 h). It is useful to compare treatments, but it is inadequate because the volume of the distribution of the solute and the time necessary to achieve an intercompartmental equilibrium are not taken into account. The frequency is the weekly elimination and is defined by the result of the elimination by the time per day-week, which makes the treatment comparable. The efficacy describes the fractional elimination of a solute given (Kt/V [where V is the volume of distribution]). Urea is commonly used in patients during end-stage disease but has not been validated for patients with AKI due to the uncertainty of the measurement of the volume of distribution. The limitation of this approximation is that it considers the dose of dialysis, only referring to the role of blood purification.

As described previously, critical patients require a more holistic evaluation, including control of the acid-base, intravascular volume, electrolytes, temperature and not for defining when dialysis is initiated, but also to evaluate whether or not it is adequate. In the final stage of the disease there is evidence that a minimal dose of Kt/V from 1.2 three times per week is adequate because an increase does not determine any improvement in the evolution; however, in AKI the effect of the dose in improvement is still controversial. Researchers in the Cleveland Clinic show that the dose affects improvement in patients with AKI when they are evaluated to be in intermediate severity and that it is irrelevant with lower degrees or higher degrees of severity. Many studies show better progression when the highest dose is used.

Shiffl et al. found that daily dialysis is associated with better evolution when compared with intermittent hemodialysis, but patients with IHD have hypotension with more frequency, which suggests that perhaps other causes in addition to the dose have an influence on improvement. Ronco et al. demonstrated an increase in survival when the continuous veno-venous postdilution hemofiltration with an effluent dose of 35-45 mL/kg/h was compared with the dose of 20 mL/kg/h. This tendency in increased survival was also true in septic patients.

The controversy resulted in acute tubular necrosis (ATN) and renal studies published in 2008 and 2009, respectively. ATN is a multicentric study in which hemodynamically stable patients are randomly assigned low or high doses of intermittent hemodialysis (three times/week vs. six times/week); hemodynamically unstable patients were randomly assigned, low or high doses of continuous renal replacement therapy (20 mL/kg/min vs. 35 mL/kg/min). Similarly, RENAL study compared the high dose (20 mL/kg/min vs. 35 mL/kg/min) against the low dose (25 mL/kg/min) in critically ill patients. Both failed to demonstrate decrease in mortality or in decrease in renal insufficiency symptoms when the highest dose was reached. In addition to the different findings of this study, the amount of stopping time during continuous renal replacement therapy should be taken into account as this significantly reduces the dose prescribed. The DO-RE-MI study was a multicenter, prospective study designed to evaluate the association between release dose and improvement. Investigators found that even if the average prescribed dose was 35 mL/kg/min, the average
release dose was 27 mL/kg/min. The main cause of treatment detention time was the closing of the conduit due to vascular access problems for clinical reasons.

The issue of adequate dose in continuous renal replacement therapy is a matter of debate; however, we can assume that the optimal dose is between 25 and 35 mL/kg/min, as higher doses provide no additional benefit. We can conclude that there is an initial phase in which the dose and improvement are directly related and any dosage increase is reflected in improved outcome. After this phase a critical point is reached and any further increase in dosage does not lead to improvement, which mainly depends on the severity of the disease. This critical point for renal replacement therapy now is 35 mL/kg/h but could increase to 45 mL/kg/h or even more in septic patients.5

In conclusion, factors related with time and dose in critically ill patients treated with renal replacement therapy are still not resolved and there is a wide variation in clinical practice due to lack of consensus. However, some key points may be defined. Given the need for absolute indication of continuous renal replacement therapy, it should be initiated as soon as possible, but if there is AKI without absolute indication for continuous renal replacement therapy, the optimization of fluid resuscitation and monitoring the disease is suggested. It is important to consider the initiation of continuous renal replacement therapy in the following cases: when diagnosis of stage 3 AKI is made or in stages 1 or 2 of AKI with rapid deterioration of renal function or with increased severity of the function renal or due to a non-renal indication. The non-renal indication for continuous renal replacement therapy is a rapidly growing area because blood purification appears to be more appropriate to restore and maintain homeostasis. Septic shock, fluid overload, electrolyte imbalance, alteration in thermoregulation, exogenous and endogenous intoxication are the most common non-renal indications for renal replacement therapy and should be taken into account when assessing its application. A standard dose of 25-35 mL/kg/h should be used, and consideration of the risk of detention time of treatment in which the prescribed dose should be 25% higher than desired to avoid subdialyzing the patient.13

References