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Acute Kidney Injury in the Intensive Care Unit

Jose J. Zaragoza and Faustino J. Renteria

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Abstract

Acute kidney injury (AKI) is defined as an abrupt decrease in glomerular filtration rate (GFR). Incidence varies from 20% to as high as 70% in critically ill patients. Classically, AKI has been divided into three broad pathophysiologic categories: prerenal AKI, intrinsic AKI, and postrenal (obstructive) AKI. The clinical manifestations of AKI vary among a wide range of symptoms and metabolic abnormalities. A sudden decrease in GFR will result in rising concentrations of solutes in the blood, which are normally excreted by the kidneys. Recently, new urinary and serum biomarkers have gained a place in the diagnosis, classification, and prognosis prediction of AKI. The best treatment for AKI is prevention. Patients with prerenal azotemia should have intravascular volume deficits corrected and cardiac function optimized. Obstructive (postrenal) kidney disease is treated by mechanical relief of the block. The primary management of acute interstitial nephritis is discontinuation of the inciting agent. Renal replacement therapy (RRT) has emerged as a supportive mechanism rather than just as a lifesaving measure. Continuous techniques are preferable in treating critically ill patients, although every modality has its benefits, indications, and contraindications.

Keywords: acute kidney injury, acute renal failure, intensive care unit, glomerular filtration rate, renal replacement therapy

1. Introduction

Acute kidney injury (AKI) is now recognized as a major health problem that affects millions of patients worldwide and leads to decreased survival and increased risk of progression to chronic kidney disease (CKD). It is often diagnosed along with other acute illnesses and is

common in critically ill patients. AKI has also an important role since it is strongly associated with augmented costs of care, worse outcomes, and diminished quality of life after discharge. The impact and prognosis of AKI vary considerably depending on the severity, clinical setting, comorbid factors, and geographical location [1].

AKI in the ICU is common, and it is increasing in incidence. Reported mortality in ICU patients with AKI varies between studies depending on AKI definition and the patient population studied. In most studies, mortality increases proportionately with increasing severity of AKI. In patients with severe AKI requiring renal replacement therapy (RRT), mortality is approximately 50–70%. Although AKI requiring RRT in the ICU is a well-recognized independent risk factor for in-hospital mortality, even small changes in serum creatinine (SCr) are associated with increased mortality.

The definition of AKI has many perceptions, the simplest way to describe it is as a sudden decrease in glomerular filtration rate (GFR) resulting in the retention of metabolic waste products and the dysregulation of fluid, electrolyte and acid-base homeostasis. AKI is a heterogeneous syndrome that includes hemodynamic disarrangements that disturb normal renal perfusion and decrease GFR without overt parenchymal injury; partial or complete obstruction to urine flow; and acute parenchymal injury resulting in glomerular, interstitial, tubular, or vascular dysfunction. The most common causes of AKI in critically ill patients include hemodynamically mediated prerenal dysfunction and acute tubular necrosis (ATN) due to ischemia-reperfusion injury, nephrotoxic exposure, or sepsis [2].

The cardinal manifestation of AKI is the retention of metabolic waste products, most commonly represented by creatinine and urea, and/or fluid accumulation. More than 35 clinical definitions of AKI currently exist in the literature. The Acute Dialysis Quality Initiative convened in 2002 and proposed the RIFLE classification (risk, injury, failure, loss, end-stage kidney disease) specifically for AKI in critically ill patients. Using SCr and urine output, the RIFLE criteria define three grades of severity and two outcome classes. Later, the Acute Kidney Injury Network (AKIN) proposed another clinical and practical definition. Even small changes in serum creatinine concentrations are associated with a substantial increase in the risk of death. For this reason, in 2012, the Kidney Disease Improving Global Outcomes (KDIGO) classification defined AKI as a raise of serum creatinine of at least 0.3 mg/dl or as a urine output of less than 0.3 ml/kg/h for at least 6 h (**Table 1**) [3].

2. Epidemiology

The epidemiology of AKI varies depending on the type and characteristics of the population described. Using the current 0.3-mg/dl change in serum creatinine threshold, published data ranges the incidence of AKI in hospitalized patients from 3 to 50% and from 10 to 70% in the intensive care unit (ICU). A 2013 meta-analysis of AKI incidence per the kidney improving global outcomes staging system with a total number of patients included of 3,585,911, reported incidence in 23% overall hospitalized patients [4].

Stage	RIFLE	AKIN	KDIGO	Urine output
RIFLE–Risk AKIN/ KDIGO Stage 1	Increase in serum creatinine × 1.5 (within 7 days)	Increase in serum creatinine of 0.3 mg/ dl or > × 1.5 (within 48 h)	Increase in serum creatinine of 0.3 mg/ dl (within 48 h) or × 1.5 (within 7 days)	Urine output of < 0.5 mg/kg/h for > 6 h
RIFLE–Injury AKIN/ KDIGO Stage 2	Increase in serum creatinine × 2	Increase in serum creatinine × 2	Increase in serum creatinine × 2	Urine output of < 0.5 mg/kg/h for > 12 h
RIFLE–Failure AKIN/ KDIGO Stage 3	Increase in serum creatinine × 3 or above 4.0 mg/dl	Increase in serum creatinine × 3 or above 4.0 mg/dl	Increase in serum creatinine × 3 or above 4.0 mg/dl	Urine output of < 0.3 mg/kg/h for > 24 h or anuria for > 12 h
RIFLE–Loss	Need for RRT for >4 weeks			
RIFLE–End stage	Need for RRT for >3 months			

Table 1. AKI definition by clinical parameters per RIFLE, AKIN, and KDIGO.

Among critically ill patients, numerous cohort studies have been issued to define the incidence of AKI in ICU. Final reports suggest that it goes as high as 70% in some populations. Patients with ICU-associated AKI are younger, more likely to be male and prone to have AKI associated with multisystem organ failure as opposed to isolated AKI. The most important recognized risk factor for AKI in the ICU environment is sepsis. Other important risk factors include previous diagnosis of Diabetes, Hypertension or CKD, concomitant use of vasopressors and use of mechanical ventilation. Renal replacement therapy (RRT) rates and mortality associated to AKI are significantly higher among ICU population opposed to hospitalized patients [5].

Two distinct patterns of ICU-associated AKI have been described: community-acquired AKI, present at ICU admission, and hospital-acquired AKI. Patients with hospital-acquired AKI have more severe outcomes, showing higher in-hospital mortality rates, longer lengths of stay both in the ICU and hospital, and higher needs of RRT [6, 7].

3. Pathophysiology

AKI can be divided into three broad etiologic categories: prerenal AKI, intrinsic AKI, and postrenal (**Figure 1**). Prerenal refers to states of hypoperfusion of the kidneys without a parenchymal damage, this kind of AKI occurs often in ICU patients. Postrenal or obstructive AKI is characterized by acute block of the urinary tract. Regarding intrinsic dysfunction, acute damage to the renal parenchyma exists, as in acute tubular necrosis, acute interstitial nephritis and/or acute glomerular nephritis. The terms "prerenal," "intrinsic," and "postrenal" are used to group common pathophysiologic features and not diagnosis. It was a long-held view that "prerenal AKI" or "transient" AKI were synonymous with "hypovolemic AKI" and "fluid responsiveness," this is no longer the case and must not be used in this manner. Approach to the diagnosis and treatment is described below [8, 9].
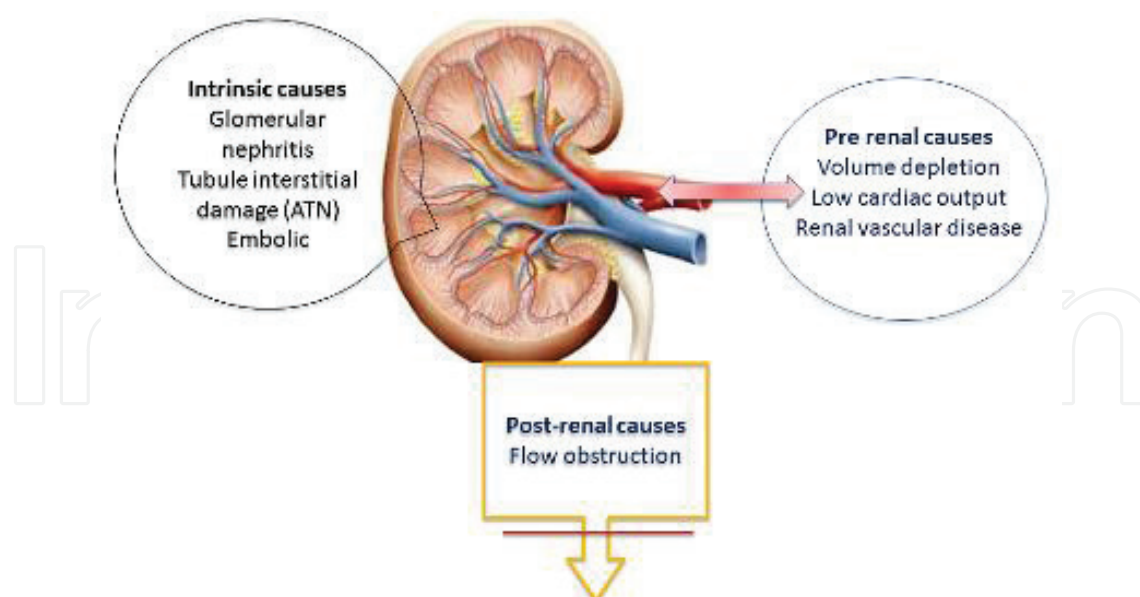
Figure 1. Traditional etiologic categories for AKI.

3.1. Prerenal AKI

Prerenal AKI is the most common pathophysiologic cause of AKI, contributing to the development 30–60% of all cases of AKI in ICU. Prerenal AKI develops when the capacity of the normal physiologic responses to hypovolemia is exceeded. This response initiates with a decrease in mean arterial pressure, triggering baroreceptors that lead the activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS), and secretion of the antidiuretic hormone vasopressin. The activation of the renal sympathetic nerves constricts the afferent (preglomerular) arterioles and stimulates release of renin from the juxtaglomerular apparatus. Renin secretion is also directly stimulated in response to hypovolemia by changes in intrarenal hemodynamic. Secretion of renin activates a cascade with the final production of angiotensin II. Angiotensin II stimulates both afferent and efferent (postglomerular) arteriolar vasoconstriction; however, the effect on the afferent vessel is opposed by vasodilatory prostaglandins, kallikrein, kinins, and nitric oxide. The net effect is vasoconstriction of both afferent and efferent arterioles and decrease of GFR to maintain circulating volume at near normal levels by the production of concentrated urine with low sodium content (i.e., fractional excretion of sodium) [10–12].

In classic forms of prerenal AKI, reduced renal perfusion pressure (or increased renal venous pressure) and afferent arteriolar constriction combined lower the glomerular capillary hydrostatic pressure below the autoregulation capacity and consequently the net ultrafiltration pressure, hence diminishing GFR. Prerenal AKI may be caused by extracellular fluid volume loss or shifts, reduced cardiac output, systemic vasodilation, intrarenal vasoconstriction, or increased renal venous pressure.

3.2. Renal AKI

Intrinsic AKI is commonly divided into tubular, interstitial, glomerular, and vascular processes depending on the nephron region that is the most affected. The most common intrinsic cause of AKI is ATN, accounting for 85–90% of intrinsic ICU-associated AKI. The causes of ATN can be broken down into three major categories: ischemia-reperfusion injury, nephrotoxic, and septic. Sepsis-associated ATN has unique features and may develop in the absence of overt renal ischemia [13].

3.2.1. Sepsis-associated ATN

Sepsis has long been recognized as a foremost precipitant of AKI and deserves a distinction. Sepsis-associated AKI (SA-AKI) portends a high burden of morbidity and mortality in both children and adults with critical illness. Observational data suggest that injury during SA-AKI occurs early of the critical illness and after ICU admission. In a large recent cohort, 68% of 5443 patients with septic shock had evidence of AKI within 6 h after presentation. The development of AKI later during an episode of sepsis has been associated with worse clinical outcome and increased mortality rates (76.5 vs. 61.5% in early AKI) [14].

Sepsis-mediated hypo perfusion leading to tubular necrosis has been traditionally cited as the main pathophysiology for SA-AKI; however, mounting evidence has challenged this paradigm. Numerous drivers for injury now are recognized as playing a role in SA-AKI, including ischemia-reperfusion injury, nephron inflammation, hypoxic and/or oxidant stress, cytokine and chemokine-driven direct tubular injury, and tubular and mesenchymal apoptosis. For instance, renal vein thermodilution measurement of RBF in eight septic critically ill patients did not show hypoperfusion to the glomerulus consistently. Tubular cellular injury contributes to the propagation of AKI during sepsis. Several causal mechanisms appear to be involved, but tubular necrosis, traditionally cited as the major cellular switch for injury, is not supported by the available experimental evidence. Renal tubular apoptosis in response to the stress of systemic sepsis now is cited as a potential contributing mechanism of injury in SA-AKI [14–16].

Similarly, cellular hypoxia is a molecular driver of injury during SA-AKI. Tissue hypoxia in the kidney during sepsis may be defined by inflammation, changes in intrarenal nitric oxide, nitrosative stress or oxygen radical homeostasis, and dysregulation. Downregulation of mediators of oxidative phosphorylation occurs during sepsis and protection of mitochondrial respiration may mitigate renal injury during sepsis [14, 17, 18].

3.3. Postrenal AKI

AKI resulting from obstruction usually causes fewer than 5% of ICU-associated AKI. Obstruction above the level of the bladder is referred to as upper tract obstruction. The development of AKI from upper tract obstruction requires the presence of bilateral obstruction or unilateral obstruction in the setting of a single functioning kidney or dysfunction of the contralateral kidney.

Patients with obstructive disease may present with anuria if obstruction is complete, with normal or increased urine volume in a partial obstruction, or with fluctuating urine output with periods of anuria alternating with rapid passage of urine as the pressure in the collecting system rises and overcomes the block. In the acute phase of obstruction, intratubular pressure rises over venous renal pressure replacing the latter in the net filtration pressure equation. When intratubular pressure reaches close to mean arterial pressure, net filtration pressure falls below the autoregulation range, sometimes almost to zero [19].

4. Clinical findings

The clinical manifestations of AKI vary from a wide range of signs and symptoms. The syndrome encompasses from laboratory abnormalities without symptoms to organ failure exhibiting fluid overload and severe electrolyte and/or acid-base disturbances [20].

A sudden decrease in GFR results in rising concentrations of waste products, commonly represented by urea end creatinine in the blood. The relationship between the GFR and the concentration of urea and creatinine in blood stream is nonlinear and may be affected by a variety of other factors. The level of blood urea nitrogen (BUN) generally correlates with the symptoms, with uremic manifestations usually absent until the BUN is above 100 mg/dl. Creatinine is derived from the nonenzymatic hydrolysis of creatine, which is usually released at a constant rate from skeletal muscle and is excreted primarily by filtration at the glomerulus. There is essentially no tubular reabsorption of creatinine. That is why, in the absence of glomerular filtration, serum creatinine typically increases by 1–2 mg/dl/day. The role of creatinine as a marker of renal function is limited by the fact that the serum concentration may take 24–36 h to rise after a renal insult. Additionally, ICU patients commonly accumulate fluid due to intravenous administration and concomitant AKI. Fluid overload decreases creatinine concentration since it dilutes the total amount of creatinine in the extracellular fluid. A true change in GFR may not be adequately reflected by serum creatinine in patients with sepsis, liver disease, fluid overload, and/or muscle wasting [20].

Urine output of less than 400–500 ml/day or a sustained urine output of less than 20 ml/h in a high-risk patient in the absence of volume depletion almost always indicates the presence of AKI. By KDIGO definition, a urine output of less than 0.5 ml/kg/h for 6 h indicates the occurrence of AKI [3].

4.1. Biomarkers

Cystatin C is a cysteine protease inhibitor that is released into the bloodstream at a constant rate from all nucleated cells. It is filtered at the glomerulus and reabsorbed and catabolized by renal proximal tubular epithelial cells such that virtually no cystatin C appears in the urine. The interindividual variability in cystatin C production appears to be less than that for creatinine. Cystatin C may be a more reliable marker of GFR [21].

Several relatively new biomarkers of tubular injury have been proposed as novel diagnostic tests for the early diagnosis of AKI. These markers include kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), liver fatty acid binding protein (L-FABP), and α- and π-glutathione-S-transferase (GST), among others. They have been tested particularly amid cardiac surgery patients, with good predicting values. Even though these markers seem promising, these are not suitable for indiscriminate use in every ICU patient, and their exact specific role at the bedside remains uncertain [22, 23].

A novel test method measures two small tubular cell–derived molecules, Insulin-like Growth Factor Binding Protein 7 (IGFBP7) and Tissue Inhibitor of Metalloproteinase 2 (TIMP-2). IGFBP7 and TIMP-2 are markers of cell cycle arrest and possibly apoptosis, inflammation, and tubular cell repair. The above-stated conditions appear to be the most relevant in the development of tubular cell injury, when the loss of cell polarity, brush border derangement, and cell sloughing might occur. Such injury may deflect the organism from normal repair toward maladaptive and lead to CKD, which further predisposes the individual to recurrent AKI [24].

According to recently published data, this test possesses the highest sensitivity for detecting AKI at an early stage. The Astute140™ meter is a device based on a fluorescence labeling technique, which detects fluorescent signals from the immunoassay and calculates concentrations of IGFBP7 and TIMP-2 from the inserted cartridge. The device converts the measured signals into a single number, defining the relative risk of the patient developing AKI. The result, known as the AKIRisk score, is obtained within 20 min [25].

5. Approach

The first step in evaluating a patient with AKI in the ICU is to determine whether kidney hypo perfusion plays a role in the current state. Physical examination should focus on assessing for evidence of volume depletion, such as dry mucous membranes, decreased skin turgor, and absence of sweat in the axilla and inguinal regions. If necessary, a more complete assessment should be done before or at the ICU. Advance hemodynamic monitoring is reasonable in high-risk patients, particularly using dynamic measurements of cardiac function, or even a complete ultrasound and echocardiographic evaluation at the bedside [26].

Placement of a bladder catheter should be performed to exclude urethra obstruction as a cause of AKI, but primarily, to initiate real-time urinary flow monitoring. Urinary output express information of whether our actions and treatment result in the patients' improvement. Urinary sediment should be examined under the microscope to discard other causes of AKI, especially intrinsic causes. In the presence of proteinuria, a urinary sediment containing abundant cells or casts suggests an intrinsic cause of AKI rather than hypoperfusion as the primary mechanism. Precisely, the presence of renal tubular epithelial cells, epithelial cell casts, or pigmented (muddy brown) granular casts suggests the diagnosis of ATN and is associated with the increased risk for bad outcomes. A normal urine sediment suggests

the presence of either a prerenal or postrenal pathophysiology of AKI, although obstructive uropathy may be associated with haematuria, pyuria, or crystalluria. The electrolyte composition of the urine may be helpful in differentiating between prerenal and ATN (i.e., fractional excretion of sodium), but not to guide the treatment [27, 28].

Imaging of the kidneys and bladder is required for the diagnosis of obstructive kidney disease and might provide information about the prehospital kidney function. Enlarged kidneys in a diabetic patient suggest that a previous damage was present, and GFR was diminished at baseline. This is especially helpful in a community-acquired AKI patient in whose previous renal function is unknown.

5.1. Clinical vs. subclinical AKI

The pitfalls of currently recommended diagnosis of AKI (i.e. creatinine and urinary flow) and the discovery of the above-mentioned new biomarkers have created new insights in AKI approach. The alteration of tubular and cellular arrest biomarkers, without creatinine elevation or a diminish of urinary flow, has led to the theory that at least some of the nephrons in the kidneys have suffered damage despite lack of azotemia (i.e. subclinical AKI). New classification for AKI has been proposed based on this. This new classification encompasses both clinical (i.e., with elevation in creatinine) and subclinical (i.e., alteration in biomarkers without creatinine elevation) AKI (**Figure 2**) [3, 23].

6. Treatment

The best treatment for AKI is acknowledging the existing risk factors and prevention. Diminish the time of hypo perfusion in every patient with AKI by a rapid recognition of cardiac output deficits, keeping an adequate intravascular effective volume and avoid nephrotoxic are keystones of prevention.

There is no specific management that accommodates the clear majority of patients with established AKI. Patients with prerenal AKI, as mentioned, should have intravascular volume deficits corrected and cardiac function optimized. Obstructive (postrenal) kidney disease is treated by mechanical relief of the obstruction. The primary management of acute interstitial

Figure 2. Clinical vs. subclinical AKI.

nephritis is discontinuation of the inciting agent; in patients with persistent AKI, there may be a role for treatment with glucocorticoids.

Once volume status and cardiac output have been optimized, if the patient remains oliguric, the use of a unique trial of diuretics to establish urine output can be considered. Although nonoliguric forms of ATN are associated with significantly lower risk of morbidity and mortality than oliguric forms, the primary rationale for a trial of diuretic therapy is to facilitate volume management not to improve AKI. None of the most common diuretics used in ICU worldwide increase the GFR. Positive fluid balance after development of AKI is associated with increased mortality rate, and avoiding fluid accumulation has a protective effect over mortality. The use of renal vasodilators, including dopamine, fenoldopam, and atrial natriuretic peptide, has not been shown to be beneficial in AKI, and its use should be discouraged [3].

AKI is associated with the development of sometimes serious electrolyte and acid-base disturbances, including hyperkalemia, hyponatremia, hyperphosphatemia, hypo- and (less commonly) hypercalcemia, hypermagnesemia, hyperuricemia, and metabolic acidosis. In addition, AKI is associated with anemia, bleeding diatheses, increased risk of infections, and dysfunction of other organ systems, including cardiovascular dysfunction, respiratory failure, gastrointestinal complications, and neurologic disturbances. These complications should be in mind of the treating physician in the ICU at every time [29, 30].

6.1. Renal replacement therapy

In patients with severe AKI, RRT is the cornerstone of supportive management. One objective of RRT includes allowing the removal of fluid and solutes that accumulate during renal failure. The available modalities of RRT comprise intermittent hemodialysis (IHD), the various forms of continuous renal replacement therapy (CRRT), and the hybrid modalities of prolonged intermittent RRT (PIRRT; also, extended duration dialysis [EDD] or sustained low-efficiency dialysis [SLED]) [31, 32].

Solute removal during RRT may occur by diffusion down a concentration gradient from the blood across a semipermeable membrane into dialysate or by convective transport of solute across the membrane during filtration. Fluid removal occurs by filtration, driven by either a hydrostatic or osmotic pressure gradient across the semipermeable membrane. In conventional IHD, the patient's blood passes through a semipermeable hemodialyzer counter current to the flow of dialysate on the other side of the membrane. The dialysis solution has a composition that approximates the normal electrolyte conformation of extracellular fluids and creates equilibrium to the blood, normalizing solutes. CRRT utilizes either diffusive hemodialysis, convective hemofiltration, or a combination of both. In addition to the duration of therapy, the major difference between intermittent and continuous hemodialysis is the dialysate flow rate. In intermittent hemodialysis, dialysate flow rates (typically 500–800 ml/min) are equal to or greater than blood flow rates, allowing rapid solute clearance. In continuous hemodialysis, the dialysate flow rate (typically 15–30 ml/min) is slow compared to that of the blood, permitting virtual equilibration of low-molecular-weight solutes such as urea between the blood and

dialysate. Thus, solute clearance for low-molecular-weight solutes approximates the dialysate flow rate. Nonetheless, the total daily or weekly clearance is greater with continuous treatment, due to the extended time of therapy.

In continuous hemofiltration, a high filtration rate is generated, and physiologic replacement fluid is administered at an equal rate. Negative fluid balance (ultrafiltration) is accomplished by administering less milliliter per hour (usually 50–400 ml/h). Solute removal occurs exclusively by convection, and clearance is approximately equal to the ultrafiltration rate. The convective transport is limited primarily by the pore size of the membrane, so hemofiltration provides more efficient clearance of higher molecular weight (>500–15,000 KDa) solutes. Although it has been proposed that removal of higher molecular weight solutes with hemofiltration as compared to hemodialysis would be of clinical benefit, this has not been borne out in clinical trials. Because of their prolonged duration, the net ultrafiltration rate required to attain the same daily fluid removal is lower with CRRT than with IHD. Thus, CRRT is generally considered to cause less hemodynamic instability than conventional IHD [33].

Finally, PIRRT is a modification of conventional IHD, utilizing lower blood and dialysate flow rates while prolonging the treatment duration to 8–16 h.

There has been considerable debate regarding which modality is most appropriate for use in critically ill patients with AKI. Current data suggest that no individual modality of RRT provides either better patient survival or recovery of kidney function. These modalities should be complementary and must not be considered as mutually exclusive. According to the KDIGO guidelines, CRRT must be considered the first-line treatment in hemodynamically unstable patients and those with neurological illness whom require RRT and might be prone to develop cerebral edema [3].

Conventional indications for initiation of RRT include volume overload unresponsive to diuretic therapy, electrolyte and acid-base disturbances refractory to medical management, severe hyperkalemia, metabolic acidosis, overt uremia, characterized pericarditis, or encephalopathy. Most of the AKI patients in the ICU do not spent enough time in the hospital to express most of these indications. Initiating RRT in a patient with some of the conventional indications is unquestionable, although the use in other cases when the alterations do not endanger life immediately is uncertain. Studies have shown conflictive results when comparing the so-called early and late initiation strategies, with no clear benefit from one over the other. Even, there is no definition of either of them. Benefits of connecting a specific patient should be opposed to the risks of the same action, and each case should be individualized. Keep in mind, the potential harms of connecting too early include unnecessary exposure to the risks related to the catheter insertion, diminishing intravascular effective volume (especially in IHD), and resources utilization that increase costs. The unwanted adverse effect of taking too long in initiating might be death [34].

7. Outcomes

The mortality rate increases with AKI, independently associated to the underlying disease and baseline characteristics. Much higher mortality rates are associated with intrinsic forms of AKI over

prerenal or postrenal disease. In severe septic-related AKI, short-term mortality rates approach 50–70% and have changed little over the past three decades. Factors associated to increased mortality risk include sepsis, male gender, advanced age, the use of RRT, degree of creatinine increase and coexistent nonrenal organ failure. For those patients who survive, AKI is associated with prolonged length of hospitalization and substantial health resource utilization [35].

More than half of patients who recover their renal function can be demonstrated to have subclinical kidney disease including modest decrements in GFR, diminished renal functional reserve, defects in tubular function and urinary concentration, and tubule-interstitial scarring on kidney biopsy [36].

8. Conclusions

AKI in hospitalized patients is a contributing factor for poor prognosis and outcomes. In critically ill patients, AKI etiologies differ, but the core one is the occurrence of renal hypo perfusion during shock states. Therefore, the best treatment of AKI is prevention. Additionally, hemodynamic optimization and diminishing offending factors are also crucial. Several modalities for RRT are available, and they should be considered complimentary. The ideal initiation timing depends on every patient's needs and benefits should be opposed to risk continuously during each patient's evolution.

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