

Management of Chronic Kidney Disease Patients in the Intensive Care Unit: Mixing Acute and Chronic Illness

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Key Words

Acute kidney injury · Cardiorenal syndrome · Cardio-pulmonary-renal interaction · Sepsis · Acute respiratory distress syndrome · Renal replacement therapy · Maintenance hemodialysis · Peritoneal dialysis

Abstract

Patients with chronic kidney disease (CKD) are at high risk for developing critical illness and for admission to intensive care units (ICU). 'Critically ill CKD patients' frequently develop an acute worsening of renal function (i.e. acute-on-chronic, AoC) that contributes to long-term kidney dysfunction, potentially leading to end-stage kidney disease (ESKD). An integrated multidisciplinary effort is thus necessary to adequately manage the multi-organ damage of those kidney patients and contemporaneously reduce the progression of kidney dysfunction when they are critically ill. The aim of this review is to describe (1) the pathophysiological mechanisms underlying the development of AoC kidney dysfunction and its role in the progression toward ESKD; (2) the most common clinical presentations of critical illness among CKD/ESKD patients; and (3) the continuum of care for CKD/ESKD

patients from maintenance hemodialysis/peritoneal dialysis to acute renal replacement therapy performed in ICU and, vice-versa, for AoC patients who develop ESKD.

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Introduction

There has been an increase in the prevalence of chronic kidney disease (CKD) during the last decades [1, 2]. Because of changes in patients demographic characteristics and availability of long-term renal replacement therapy (LT-RRT) during end-stage kidney disease (ESKD), the percentage of patients with preexisting renal dysfunction who develop acute critical illness, requiring admission in the intensive care unit (ICU), is progressively increased [3]. Nowadays, the management of 'critically ill CKD patients' is a routine clinical challenge for nephrologists and intensivists. Indeed, several epidemiological studies have shown preexisting renal dysfunction to be a significant cause for increase in risk of death, particularly for those patients admitted in the ICU [4].

The development of acute kidney injury (AKI) in CKD patients during acute illness is quite common (acute-on-chronic (AoC) kidney disease) and further worsens the patient outcome [3]. Nonetheless, for those patients who survived from critically ill AKI after an AoC episode, the risk for progression of the kidney dysfunction is high and frequently leads to ESKD [3]. The relationship among AKI, CKD and ESKD is highly complex. During the past decades, nephrologists and intensivists have classified the acute and chronic renal dysfunction as two separate clinical syndromes. Nevertheless, although this conceptual distinction might allow a more feasible and organized approach to clinical research and trial, those two syndromes have been identified in several epidemiologic and pathophysiological studies not only as distinct entities but also mainly as closely interconnected [5]. Common pathophysiological mechanisms leading to kidney damage might result in the development of AKI and worsening of CKD in the patients, thus causing ESKD and acting as major risk factors for non-renal acute or chronic organ dysfunction.

Taking into account the high prevalence and mortality rate of CKD patients in the ICU, the incidence of AoC kidney dysfunction in those patients and the rate of progression toward ESKD, an integrated multidisciplinary effort should be advocated. Indeed, an adequate management of multi-organ damage of those kidney patients, thereby preventing the progression of kidney dysfunction during their critically illness is thus necessary [3].

The aim of this review was to describe (1) the pathophysiological mechanisms underlying the development of AoC kidney dysfunction among CKD patients and its role in the progression toward ESKD; (2) the most common clinical presentations of critical illness among CKD/ESKD patients; and (3) the continuum of care for CKD/ESKD patients from LT-RRT to acute renal replacement therapy (A-RRT) performed in the ICU and, vice-versa, for AKI patients who develops ESKD.

Immunologic and infective problems related to kidney transplantation lead to peculiar clinical settings, which requires a specific and separate dissertation. An extensive analysis of AoC kidney dysfunction developed on kidney transplanted patients is beyond the aims of this review.

Pathophysiological Relationship between CKD and AKI

Several pathophysiological mechanisms link the development of AKI with preexisting CKD, potentially explaining the high incidence of AoC kidney dysfunction

among kidney patients admitted in the ICU. On the other hand, the acute insult that occurred in the ICU, which led to AKI, and its maladaptive repair may accelerate the progression of CKD patients toward ESKD.

CKD Patients Who Develop AKI

With an increased risk by as much as ten times, CKD is the major risk factor for AKI development [6, 7], particularly among critically ill patients admitted in the ICU [3]. Although fluid overload and muscle wasting may affect the reliability of serum creatinine (sCr) values in diagnosing AKI and staging its severity in critically ill patients [8], a transient decrease in renal function, consistent with AKI, might be still recognized in most critically ill CKD patients. This AoC kidney dysfunction might be caused due to several mechanisms, including failure of auto-regulation, abnormal vasodilation and adverse effects related to diuretics, antihypertensive agents and/or nephrotoxins [5] (fig. 1). Furthermore, the reduction of renal functional reserve (RFR) may increase the susceptibility of CKD patients to develop AKI [9], as well as the organ cross-talk feedbacks, in which the development of non-renal organ dysfunctions due to or associated with CKD might lead to AKI.

RFR is the amount of renal clearance capability potentially available to counteract a metabolic stressful event [10]. It might be quantified through the glomerular filtration rate (GFR) increase due to a kidney stress test, such as a protein load [11, 12]. Although still present, RFR is progressively reduced in worsening the stage of CKD [13]. In line with the RFR reduction, the extent of the minimum metabolic insult able to overcome the maximum achievable renal clearance is progressively decreased. In this context, the susceptibility of each CKD patient to develop AKI is directly proportional to the RFR reduction [10] (fig. 1).

Beyond RFR, organ cross-talk (and mainly the cardiopulmonary-renal interaction) might explain the reason behind the high incidence of organs dysfunctions in patients with CKD and their high incidence of AoC kidney dysfunction in the ICU. These interactions with pulmonary and cardiac functions are the most established in literature [14] (fig. 1).

As a matter of fact, CKD patients are at high risk to develop acute respiratory failure (fig. 1, panel A). Beyond the most intuitive mechanisms involving fluid overload and susceptibility to sepsis, several pathophysiological pathways might explain the high incidence of acute or AoC respiratory failure leading to ICU admission for these patients. As example, CKD has a major role to play

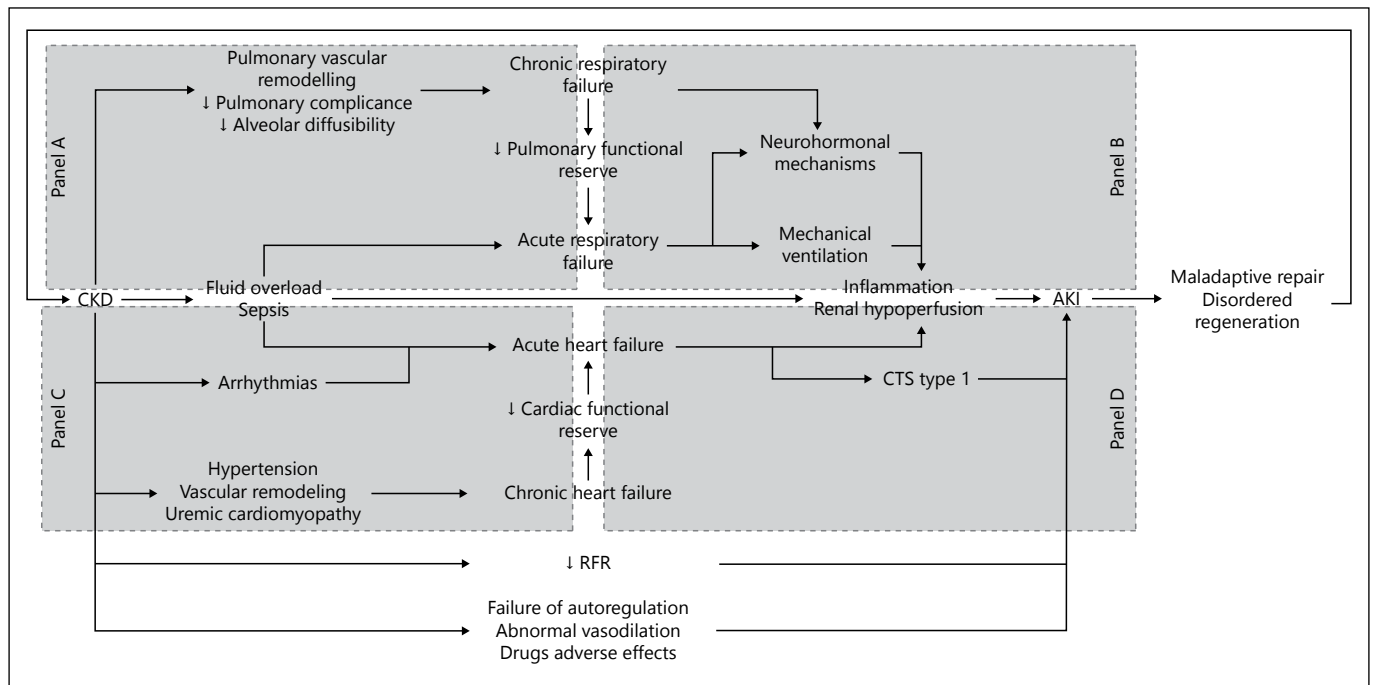


Fig. 1. Pathophysiological relationship between CKD and AKI. The maladaptive repair and the disordered regeneration are the principal mechanisms involved in the progression from AKI to advanced stages of CKD. However, critical CKD patients may present a transient decrease in renal function, consistent with AKI.

The AoC kidney dysfunction might be due to several mechanisms, including failure of autoregulation, abnormal vasodilation and adverse effects related to diuretics, antihypertensive agents and/or nephrotoxins, but also due to the reduction of RFR.

in the development of pulmonary hypertension [15] leading to pulmonary vascular remodeling through pathophysiological mechanisms involving endothelial dysfunction, decreased bioavailability of nitric oxide, increased levels of endothelin-1, fluid overload, and shunting via arterio-venous fistulae [16]. Furthermore, a lung structural remodeling might be recognized in CKD patients, mainly characterized by the proliferation of fibroblasts with fibrosis and extracellular matrix deposition, resulting in the thickening of the alveolar wall [14]. In addition to the uremia-related dysfunction of the pulmonary microcirculation, these mechanisms might cause a restrictive, poorly compliant lung with impaired gas exchange [17]; moreover, the reduction in diffusion capacity for carbon monoxide correlates with the severity of renal impairment in CKD patients [18]. All these mechanisms might reduce the lung functional reserve leading to increased susceptibility for acute respiratory failure and ICU admission.

As soon as the CKD patient develops acute or AoC respiratory failure, the possibility to AKI occurrence is exponentially increased. Several mechanisms sustained by organ cross-talk might lead to AKI that is caused due to

non-renal organ damages (fig. 1, panel B). For example, most of patients with respiratory failure admitted in the ICU undergo mechanical ventilation that might impact the renal function; the hemodynamic effects of mechanical ventilation potentially leading to kidney hypo-perfusion are well established in literature [19]. In particular, positive pressure ventilation might lead to an increase in intra-thoracic pressure, a reduced venous return, an increased vascular resistance in pulmonary circulation, right ventricular failure, cardiac septum shift, reduced left ventricle preload, reduced cardiac output, hypotension and peripheral hypo-perfusion. All these hemodynamic effects might occur in patients with an already reduced kidney perfusion, directly related to the cause of respiratory failure (e.g. intra-abdominal hypertension [10]), or for the concomitant alteration of neuro-hormonal pathway (e.g. those aiming to retain salt and water to maintain an adequate vascular filling pressure to counteract the peripheral vasodilation due to hypercapnia [20, 21]). Furthermore, a well-established pro-inflammatory effect of mechanical ventilation has been associated with an increased susceptibility to develop clinical or subclinical AKI [22]. Indeed, the production of inflammatory me-

diators, the expression of nitric oxide synthase, the induction of renal epithelial cell apoptosis, and the dysregulation of renal vascular response have all been demonstrated to be associated with mechanical ventilation [22]. The more RFR is reduced, the more precocious, severe and persistent is the kidney damage that occurred subsequently in all these mechanisms.

Furthermore, CKD has been reported in up to 63% of cases of heart failure [11]. An accelerated coronary artery atherosclerosis has been reported during CKD, through several mechanisms, such as hypertension, dyslipidemia, altered calcium/phosphorus metabolism, vascular remodeling and increased vascular stiffness [14]. Uremic cardiomyopathy also plays a role in the structural and electrophysiological heart remodeling, leading to biventricular hypertrophy, systolic and diastolic dysfunction, capillary rarefaction and cardiac fibrosis [23]. The AoC uremic pericarditis with sterile effusion is a classical manifestation, although its occurrence is uncommon since the introduction of dialysis [14]. Beyond these mechanisms, several factors might relate to the incidence of acute heart failure to CKD (fig. 1, panel C).

The development of acute heart failure is a pivotal and progressive condition that leads to distant organ damage, due to inter-organ cross-talk, whose severity is often proportional to the duration of heart failure [14]. In these conditions, AKI occurs in about 25–33% of cases of acute decompensated heart failure (i.e. cardiorenal syndrome type 1) [24], while in 60% of them, an AoC kidney dysfunction might be diagnosed [25]. Similarly based on information reported about the lung during respiratory failure, an impairment in cardiomyocytes potentially promotes distant organ damage (i.e. AKI); potential pathophysiological mechanisms include ischemic and mechanical injury via innate immune system response, neuro-hormonal signaling and release of metabolic products (i.e. catalytic iron) [24] (fig. 1, panel D).

AKI Patients toward CKD

The analysis of the pathophysiological continuum between AKI and CKD also takes into account the long-term worsening of the kidney function due to AKI. Several studies have underlined the incidence, causes and pathophysiological mechanisms of CKD/ESKD development after single or repetitive episodes of AKI [5]. These studies have consistently demonstrated that even when the renal function recovers after the acute insult, most patients with AKI progress to advanced stages of CKD. Interestingly, this progression occurs even in the

absence of common risk factors (such as hypertension, diabetes, or cardiovascular disease [26]), during mild cases and regardless of the cause of AKI [5]. Although several pathophysiological mechanisms leading to progression of renal damage in humans have been postulated in literature [5], the final causal pathways involved in the ongoing organ dysfunction seem to include maladaptive repair, disordered regeneration, or both [27, 28] (fig. 1).

CKD/ESKD Patients Admitted in the ICU

Advanced age, the higher prevalence of peripheral vascular disease, cerebro-vascular disease, ischemic and non-ischemic cardio-vascular disease and diabetes mellitus complicate the care provided to CKD/ESKD patients. A recent systematic review has shown that cardiopulmonary edema and sepsis are the most frequent causes for ICU admission [29]. Common triggers of cardiopulmonary edema could be represented by pneumonia, excessive inter-dialytic weight gain, inappropriate prescription, but also primary cardiac events [30]. CKD/ESKD is associated with an increased incidence of critical illness and with a greater risk of morbidity and mortality after major surgical procedures [31].

Clinical Pictures

Cardiovascular Disease

Myocardial infarction, cardiac arrest and malignant arrhythmias are the major causes of sudden death in CKD/ESKD patients, accounting for 43% of all-cause mortality [32]. CKD/ESKD patients often present with left ventricular hypertrophy, arrhythmias due to rapid electrolyte shifts during LT-RRT, QT dispersion, sympathetic over-activity and cardiovascular deposition of calcium-phosphate [32]. CKD/ESKD patients with or without residual renal function experience a condition where there is failure of salt and water excretion and this may result in chronic hypertension. Acute pulmonary infection, excessive inter-dialytic weight gain, inappropriate dry weight prescription, and primary cardiac events are common triggers for acute pulmonary edema [33]. Cardiac output monitoring for fluid management, vasoactive therapy, nitrate infusion and continuous positive airway pressure may be promptly required, avoiding harmful delay in A-RRT initiation [30]. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T values are of less diagnostic value in the acute setting in CKD/ESKD patients. Indeed, serum levels of

troponin T and NT-proBNP are already elevated in those patients [34] and potentially affected by the modality of LT-RRT, the use of catheter or graft [35] and high-flux dialyzers that may increase their clearance.

Infectious Processes

Following cardiovascular disease, sepsis is the second cause of death in patients with CKD/ESKD [36]. A particular 'resistance profile' to antimicrobial therapy can challenge the initial approach, but also the management, thereby increasing the risk of failure and the costs of care [37]. The high risk of infection is due to attenuated acute inflammatory and immunological responses [37, 38], such as impairment of phagocytic function [39]. Comorbidities (e.g. diabetes), anatomical abnormalities (e.g. polycystic kidney) and repetitive exposures to nosocomial microorganisms can increase the risk of the occurrence of sepsis [40]. The most common source of infection is represented by indwelling catheters followed by lower respiratory tract infections [41], cellulitis and pyocystis [42, 43] as well as the breaching of cutaneous barriers. Catheters and prosthetic arteriovenous grafts represent a nidus for infection. Hemodialysis (HD) catheters are often responsible for the onset of early infectious complications [44], while peritoneal dialysis (PD) catheters cause not only a higher rate of late infectious complications, but also higher mortality [45]. *Escherichia coli* and *Staphylococcus epidermidis* are the most common microorganisms [46]. The diagnosis of sepsis is a clinical challenge in CKD/ESKD patients. The sepsis management is based on early goal-directed therapy [47]. Previous studies examining patients with sepsis in LT-RRT have concluded that volume resuscitation should proceed with the same measurement and goals as non-CKD/ESKD patients [48]. However, these patients usually appear to be overloaded and severely hypotensive. For this reason, physicians often regret to perform an aggressive fluid resuscitation causing under-resuscitation and a severe microcirculation impairment. An invasive hemodynamic monitoring and an adequate hydration associated to fluid removal through A-RRT should be performed. Empiric antibiotics must cover both gram-positive (e.g. glycopeptide or cephalosporin) and gram-negative organisms (e.g. third generation cephalosporin or aminoglycoside) [49], until the isolation of microorganism. Methicillin-resistant *Staphylococcus aureus* cover may be needed if the patient has an indwelling HD or PD catheter [50]. Peritonitis is a significant complication of PD with a mortality of 3.5–10% [51]. It is defined by the presence of sign and symptoms, a white cell count >100/ml of PD effluent and >50%

neutrophils after a dwell of at least 2 h and a positive culture of an organism from the PD effluent [49]. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common organisms implicated in the prevalence of peritonitis of PD.

Major Surgical Procedures

Data on the possible impact of CKD/ESKD on outcome after major surgical procedures are scarce and for this reason it is not possible to perform a risk stratification of surgical patients. Patients with residual renal function before surgery and post-operative anuria have higher mortality than patients with no residual renal function before surgery or with residual renal function before and after surgery. Postoperative urine output is an important surrogate marker for kidney disease severity [52]. In addition, perioperative hemodynamic status and biochemical factors are also related to a patient's mortality [53].

Management

In the intensive care environment, the A-RRT prescription and management for CKD/ESKD patient depend on several factors, such as modality and access of pre-existing LT-RRT, hemodynamic status, physician and staff experience and ICU resources. The less use of acute PD is due to absolute or relative contraindications. Currently, most patients receive intermittent HD (IHD) or continuous renal replacement therapy (CRRT) using a temporary vascular access catheter [54].

The target point of management (table 1) is represented by the following.

Volume Status Control

The volume management in CKD/ESKD patients with sepsis, acute respiratory distress syndrome or after surgery is not a flexible process and it often requires the use of A-RRT. The CKD/ESKD patients admitted in the ICU may have a low effective arterial blood volume and hemodynamic instability, requiring the administration of intravenous fluids. When it is possible, the use of isotonic fluids to maintain a normal serum sodium concentration and tonicity is preferable. In addition, hypotonic infusions (e.g. vasopressors) and certain antibiotics administered in 5% dextrose should be predicted [54]. It is important to assess weight, fluid intake and output as well as monitor central venous pressure, central venous oxygen saturation on a daily basis, and if possible hemodynamic invasive monitoring also needs to be performed. Noninvasive methods such as bioimpedance [55–58] and

Table 1. Management of ESKD patients in ICU

Volume status control	<ul style="list-style-type: none"> – Administer isotonic fluids to maintain a normal serum sodium concentration and tonicity – Perform a daily assessment of weight, fluid intake and output – Monitor central venous pressure, central venous oxygen saturation – Perform hemodynamic invasive monitoring
Electrolyte control	<ul style="list-style-type: none"> – Consider insulin and salbutamol to treat hyperkalemia and initiate A-RRT promptly – Avoid hypokalemia during RRT because of risk of cardiac arrhythmias – Hypotonic hyponatremia, hyperphosphatemia and hypocalcemia are frequent – Hypercalcaemia may be a consequence of excessive calcium supplementation or related to the underlying cause of renal failure
Dialysis access and vein preservation	<ul style="list-style-type: none"> – Consider absolute and relative indication to PD catheters use – Avoid arteriovenous fistulas and grafts for CRRT, but consider it for IHD or hybrid therapies in ICU, if necessary – Avoid the placing of identification bands or restraints over the fistula – An internal jugular line for short-term or tunneled access is recommended – Minimize venipuncture, limit placement of peripherally inserted central catheter and avoid the use of subclavian venous site
Hemostasis	<ul style="list-style-type: none"> – Bleeding diatheses are frequent because of platelets dysfunction and extracorporeal therapies – Low-molecular-weight heparin to maintain patency of the extracorporeal dialysis circuit is of similar efficacy and safety to unfractionated heparin – Sodium citrate may be used for ‘regional anticoagulation’ where systemic anticoagulation is undesirable – Administration of vasopressin analogues and/or conjugated estrogens may complicate the management
Imaging	There is no need to perform HD immediately after radiocontrast administration
Drug use and adjustment	<ul style="list-style-type: none"> – Consider reduced GFR, the altered protein binding, the variable volume of distribution and the RRT mode when you prescribe a drug – The required dose of propofol should be titrated to effect and it is better to avoid continuous infusion of Midazolam – Morphine and Fentanyl accumulate in renal failure and it should be used with caution. Remifentanyl has no toxic effect – The continuous infusion of Furosemide has greater effect, but the increasing of diuretic dosage may cause diuretic resistance. The concurrent use of a thiazide diuretic may improve loop diuretic responsiveness – Avoid undertreatment, adverse effects but also consider pharmacokinetic/pharmacodynamic and extracorporeal clearance prescribing an antibiotic

ultrasonography techniques [59, 60] have demonstrated their diagnostic value in both CKD/ESKD and critically ill patients.

Electrolyte Control

CKD/ESKD patients, because of their limited capacity to maintain homeostatic control, present with disorders of potassium, sodium, calcium, magnesium and phosphate. The over administration, the reduced excretion or the leakage from intracellular pools may prompt to the development of life-threatening hyperkalemia with the need of pharmacologic and/or dialytic intervention [61]. Combination treatment of hyperkalemia with insulin and

salbutamol is synergistic and safe in patients with CKD/ESKD [62]. In addition, treatment with A-RRT needs to be instituted promptly. If A-RRT is delayed, the ESKD patient may experience ‘rebound hyperkalemia’ as the potassium ions return into the extracellular space but are not excreted by the kidneys [61]. Conversely, hypokalemia during RRT should be avoided because of the risk of cardiac arrhythmia and careful monitoring of potassium levels should be advocated [63]. The loss of ability to excrete a free-water load predisposes to the development of moderate-to-severe hypotonic hyponatremia. Such patients are also susceptible to the development of hyperphosphatemia and hypocalcaemia related to disorders in

calcium-phosphate metabolism. In addition, the use of citrate anticoagulation for RRT may exacerbate underlying hypocalcaemia due to the chelation of serum calcium [64]. On the contrary, hypercalcaemia may be a consequence of excessive calcium supplementation or may be related to the underlying cause of renal failure such as multiple myeloma.

Dialysis Access and Vein Preservation

– PD catheters:

Sepsis represents an absolute contraindication for PD use [65]. On the contrary, the presence of intra-abdominal foreign bodies, peritoneal leaks, inflammatory or ischemic bowel disease, abdominal wall or skin infection and severe malnutrition points to all relative contraindications to performing PD [65]. Thus, the use of PD catheter after an ICU admission is generally reduced.

– Arterio-venous fistulae and grafts:

Vascular access for CRRT should be avoided because of the increased risk of laceration of the vessel wall or of dislodgment of the return needle leading to severe or fatal exsanguination. The placing of identification bands or restraints over the fistula should be avoided. Arterio-venous fistula might be used for IHD or hybrid therapies in ICU, if necessary.

– Hemodialysis catheters:

Vascular cannulation in patients on maintenance HD may be challenging because of limited venipuncture sites due to infection, thrombosis and/or stenosis of previous catheters. An internal jugular line for short-term or tunneled access is recommended [66].

– Vein preservation: minimize venipuncture and placement of peripheral inserted central catheters and subclavian venous catheters should be avoided because of increased risk of stenosis or thrombosis. In addition, subclavian could be a future site for long-term vascular access.

Hemostasis

CKD/ESKD patients exhibit a slightly different pattern of coagulopathies than general population. CKD/ESKD patients develop hemostatic disorders mainly in the form of bleeding diatheses from hemorrhage of cutaneous sites until it leads to retroperitoneal or intracranial hemorrhages. Platelets dysfunction (impaired adhesion and decreased aggregation) is the main factor responsible for causing this condition [67]. Extracorporeal therapies (IHD, hybrid therapies and CRRT), which are able to partially correct these defects, can contribute to bleeding too. HD is also associated with thrombosis due to chronic

platelet activation because of contact with artificial surfaces during dialysis [67]. The efficacy and safety of low-molecular-weight heparin to maintain the patency of the extracorporeal dialysis circuit is similar to those of unfractionated heparin in maintenance HD patients. Sodium citrate may be used for ‘regional anticoagulation’ of the extracorporeal circuit in instances where systemic anticoagulation is undesirable [68]. The administration of vasopressin analogues and/or conjugated estrogens may complicate the management of a critically ill patient, particularly following trauma or in a postoperative setting [67].

Imaging

Performing HD immediately after iodinated contrast administration does not reduce the risk of AKI [69]. Iodinated contrast represents a combined vaso-constrictive and oxidant stress and even low (circa 600 mOsm/kg) or iso-osmolar formulations can constitute a significant volume challenge compromising pulmonary function or exacerbating right heart overload. However, in a vast majority of patients with ESKD, who are adequately dialyzed, there is no need to perform HD immediately after radiocontrast administration [70].

Drug Use and Adjustment

Drug prescription must take into account a reduced GFR, an altered protein binding and a variable volume of distribution. In addition, the mode of RRT used is the key determinant of drug dosage.

– Anesthesia and sedation:

The total propofol clearance is not influenced by CRRT, while the hemodilution or the albumin adsorption could decrease its plasma concentrations [71]. For this reason, the required dose of propofol should be titrated to effect. Midazolam is metabolized from the liver to its active metabolite, α 1-hydroxymidazolam. During a renal impairment, the elimination of α 1-hydroxymidazolam and the protein binding of midazolam is reduced [72]. The removal of midazolam through CRRT is not efficient. Bolus doses of midazolam should therefore be reduced and titrated according to the effect it causes in CKD/ESKD patients. In addition, the use of midazolam infusions in critically ill patients with ESKD should therefore be avoided, where possible. Although morphine use is not an absolute contraindication in ESKD, it should be used with caution. Morphine and its glucuronides are eliminated via the kidneys, and thus end up in renal failure [73]. A minimal amount of morphine could be removed during hemofiltration or hemodiafiltration, while a

significant quantity of free morphine may be removed in HD due to a much higher dialysate flow rate [74]. Although the use of fentanyl is often preferred in patients with renal impairment [75], dose reduction is necessary because accumulation of this drug will result in toxicity [76]. Moreover, fentanyl is not cleared by HD. Remifentanyl clearance is clinically independent of renal function, but its metabolite, remifentanyl acid, results in renal failure without a toxic effect [77].

– Diuretics:

Diuretics are limited for CKD and for those ESKD patients with urine output. PD patients more than HD patients have some residual renal function. It is well known that several features of kidney dysfunction can reduce diuretics efficacy (i.e. decreased renal blood flow and clearance, metabolic acidosis, hyperuricemia, high levels of organic anions, etc.). Moreover, in an ICU setting, malnourishment and trans-capillary leak may lead to hypo-albuminemia and increase in distribution volume, which further worsen diuretic resistance. Therefore, in critically ill CKD patients, diuretics dose should be progressively increased according to CKD stage and potential causes of diuretic resistance should be treated. Furthermore, the concurrent use of a thiazide diuretic in addition to a loop diuretic to inhibit downstream NaCl reabsorption may improve loop diuretic responsiveness [78].

– Antibiotics:

Drug dosage adjustment should take into consideration the peculiar pharmacokinetic/pharmacodynamics characteristics of critically ill patients but also the superimposed extracorporeal clearance due to A-RRT (e.g. dose, modality, etc.) [54]. The issue of antimicrobial adjustment should be considered in those critically ill CKD/ESKD patients in order to avoid under-treatment (and thus eradication failure and antimicrobial resistance occurrence) and adverse effects (such as nephrotoxins for several antibiotics).

Transition from IHD or PD to CRRT

Despite kidney transplantation is now considered the optimal treatment for most ESKD patients [79, 80] and conservative care has been demonstrated to have more or similar advantages in frail elderly patients [81], IHD remains the most common treatment for ESKD worldwide, followed by PD. IHD and PD patients are prone to repeated hospital and, to a lesser extent, ICU admissions [82, 83]. When an ESKD patient is admitted in the ICU,

the most beneficial and appropriate RRT modality should be selected. Unfortunately, the decision is made not only based on a patient's need, but also based on organizational characteristics, such as availability of technological and human resources and expertise of staff. Nowadays, CRRT is the predominant RRT modality used in Australia and in most European countries and its use in the United States is increasing [84–87]. Considerations about clinical conditions requiring CRRT in ESKD patients do not differ from those prevailing among the general population.

First used in ICU patients intolerant of IHD, CRRT maintains a key role in the treatment of hemodynamically unstable patients, in which a better dialysis tolerance is guaranteed by the slower fluid removal and the absence of fluid shifts secondary to the rapid solute removal [66]. In ICU patients who are hemodynamically stable, a Cochrane meta-analysis failed to demonstrate the superiority of CRRT over IHD for most relevant outcomes, such as mortality; however, patients treated with CRRT achieved better hemodynamic parameters [88]. The use of PD in ICU unstable patients, despite being theoretically convenient, has limitations, such as the lower efficiency, the unpredictability of fluid removal, the risk of infection and the potential interference with mechanical ventilation [89].

The other specific situation in which the transition from IHD to CRRT is mandatory is when intracranial hypertension and/or acute brain injury [66] occurs. In fact, IHD has been associated to further increases in intracranial pressure [90]. In addition, CRRT has been demonstrated superior to PD to avoid hyponatremia and thermal losses [91].

In more recent years, hybrid therapies, such as sustained low-efficiency dialysis, extended daily dialysis and prolonged intermittent RRT have developed. They seem a viable alternative to CRRT and IHD, combining advantages from both modalities (i.e. hemodynamic stability of CRRT, early rehabilitation and lower anticoagulant use of IHD). Despite these theoretical advantages and the promising results, the precise role of hybrid techniques should be further investigated with randomized controlled trials [92, 93].

Finally, in clinical settings where blood purification requirement is accompanied with multiple organ failure or septic shock, CRRT is recommended [94].

When the RRT modality is selected, an individualization of nutrition as well as a dose adjustment of prescribed drugs (i.e. antibiotics, antifungal agents, etc.) should be taken into account [66]. Although there are no available

recommendations to modify drugs dose in a given patient with a given RRT modality, a deep knowledge of both dialysis techniques and kinetic of different drugs may drive clinicians to prescribe the adequate drug dosage and dosing intervals [95, 96]. Moreover, monitoring the plasma level of drugs, when available, may help to further individualize therapy, avoiding under or overdosing.

Transition from CRRT to IHD or PD

In hemodynamically stable patients, studies failed to demonstrate the superiority of one RRT modality over the others, while both CRRT and IHD are shown to guarantee an adequate metabolic control [88, 97, 98]. Therefore, IHD or hybrid therapies may be preferred for patients who achieved hemodynamic stability, do not have acute brain injury and do not need extracorporeal multiple organ support therapy. In fact, intermittent dialysis modalities allow patients mobilization and/or rehabilitation and, finally, ICU discharge [94].

When the critical illness has been solved, patients who were on maintenance IHD or PD before the ICU admission can progressively restart their previous therapy. An exception is represented by cases in which the acute event (i.e. abdominal injury) determined an extensive loss of peritoneal surface, leading to the impossibility to perform PD.

AKI patients who do not regain normal renal function and require chronic RRT should be subjected to a dialysis modality (IHD or PD) according to patients' clinical and individual needs.

While transiting from CRRT to intermittent RRT, the same considerations discussed above about nutrition and drugs dose should be taken into account.

Recovery from AKI and Risk to Develop CKD

Once the acute kidney insult has been solved, renal function may be fully, partially or not recovered at all and various degrees of CKD, until ESKD requiring maintenance RRT, may persist. The exact rate and the pathophysiological pathways of progression to CKD are still under investigation [99]. Although there are some evidences that patients initially treated with CRRT have a lower rate of ESKD requiring maintenance RRT [100, 101], a recent, large, single-center retrospective study found no difference in renal recovery rate between CRRT and IHD as initial RRT modality [102]. RRT should be

discontinued when renal recovery is adequate to allow a sufficient metabolic, electrolyte and fluid balance [94]. The right timing is unknown and some markers have been proposed to drive RRT weaning. The most used clinical criteria are sCr levels with a constant dialysis dose and urine output [103]. Recently, daily urinary urea excretion (24 h-urinary urea, 24h-UU) and daily urinary creatinine excretion (24 h-urinary creatinine, 24h-UCr) have been evaluated in 2 different single-center retrospective studies. Both have been demonstrated to be superior than other markers and 24h-UCr than 24h-UU in predicting RRT weaning success [104, 105].

Conclusion

A large number of subjects present with a clinically manifested CKD at the time of ICU admission. In the wide spectrum of CKD, however, we must also consider subclinical forms of renal insufficiency (reduction of RFR) and on the other hand, consider patients already on ESKD and chronic dialysis treatment.

These patients suffer from increased risk of complications due to the important comorbidities that occur due to the effect of chronic kidney dysfunction. Some of these patients present with a worsening of renal function that should be defined as AoC kidney injury.

Specific complications with increased mortality and ICU length of stay have been described in patients developing de novo AKI. What has recently emerged, however, is that patients suffering from one or more AKI episodes may present a significantly higher risk to develop CKD and ESKD in the follow-up period of months or years.

All these aspects drive home the point that a multidisciplinary approach is required to treat a critically ill patient with kidney problems: preventive and protective strategies to avoid further AKI episodes should be implemented, while treatment should be optimized not only toward adequate renal replacement and support but also toward full recovery of renal function. The nephrologist and the intensivist should work together to share information and knowledge on these patients with complex conditions and should implement a common strategy to minimize complications and negative short- and long-term outcomes.

Disclosure Statement

The authors declare no conflict of interest.

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