SECTION 30

# Special Kidney Problems in the Intensive Care Unit

CHAPTER 214

## Management of Chronic Kidney Disease and End-Stage Kidney Disease Patients in the Intensive Care Unit

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**OBJECTIVES**

This chapter will:

1. Describe the pathophysiologic mechanisms underlying the development of acute-on-chronic (AoC) kidney dysfunction and its role in the progression toward end-stage kidney disease (ESKD).
2. Identify the most common clinical presentations of critical illness among chronic kidney disease (CKD)/ESKD patients.
3. Detail the continuum of care for CKD/ESKD patients from maintenance hemodialysis/peritoneal dialysis to acute renal replacement therapy performed in an intensive care unit and, vice-versa, for AoC patients who develop ESKD.

Prevalence of chronic kidney disease (CKD) has risen progressively 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), has progressively increased.[3] The management of "critically ill CKD patients" is a routine clinical challenge for nephrologists and intensivists. Indeed, several epidemiologic studies have shown for preexisting renal dysfunction a significant 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 extremely frequent (acute-on-chronic [AoC] kidney disease) and further worsens the patient outcome.[3] Nonetheless, for those patients who survived after being critically ill 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 dysfunctions as two separate clinical syndromes. Nevertheless, although this conceptual distinction may allow a more feasible and organized approach to clinical research and trial, those two syndromes have been identified in several epidemiologic and pathophysiologic studies not only as distinct entities but also mainly as closely interconnected.[5] As a result of a common pathophysiologic mechanism leading to kidney damage, the repeated AoC episodes may occur, leading to worsening of CKD until ESKD and acting as a major risk factor for nonrenal 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 multiorgan damage of CKD critically ill patients is necessary to prevent the progression of kidney dysfunction.[3]

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

### PATHOPHYSIOLOGIC RELATIONSHIP BETWEEN CHRONIC KIDNEY DISEASES AND ACUTE KIDNEY INJURY

Several pathophysiologic mechanisms link the development of AKI with the 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 leading to AKI in the context of critical illness, and

its maladaptive repair, may accelerate the progression of CKD patients toward ESKD.

## Patients with Chronic Kidney Disease Who Develop Acute Kidney Injury

Increasing risk by as much as 10 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 value in diagnosing AKI and staging its severity in critically ill patients, a transient decrease in renal function still may be recognized in most critically ill CKD patients. This transient form of AoC kidney dysfunction may be due to several mechanisms, including failure of autoregulation, abnormal vasodilation and adverse effects related to diuretics, antihypertensive agents, and/or nephrotoxins[5] (Fig. 214.1). Furthermore, the reduction of renal functional reserve (RFR) may increase the susceptibility of CKD patients to develop AKI,[8] as well as the organ cross-talk feedbacks, in which the development of nonrenal organ dysfunctions resulting from or associated with CKD may lead to AKI.

RFR is the amount of renal clearance capability potentially available to counteract a metabolic stressful event.[9] It may be quantified through the glomerular filtration rate (GFR) increase resulting from a kidney stress test, such as a protein load.[10,11] Although still present, RFR is reduced progressively in worsening stage of CKD.[12] In line with the RFR reduction, the extent of the minimum metabolic insult able to overcome the maximum achievable renal clearance is decreased progressively. In this context, the susceptibility of each CKD patient to develop AKI is directly proportional to the RFR reduction[9] (see Fig. 214.1).

Beyond RFR, organ cross-talk (and mainly the cardiopulmonary-renal interaction) may explain the high incidence of organ 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 the literature[13] (see Fig. 214.1).

As a matter of fact, CKD patients are at high risk to develop acute respiratory failure (Fig. 214.1, Panel A). Beyond the most intuitive mechanisms involving fluid overload and susceptibility to sepsis, several pathophysiologic pathways may explain the high incidence of acute or AoC respiratory failure leading to the ICU admission for these patients. For example, CKD has a major role in pulmonary hypertension development leading to pulmonary vascular remodeling through pathophysiologic mechanisms involving endothelial dysfunction, decreased bioavailability of nitric oxide, increased levels of endothelin-1, fluid overload, and shunting via arteriovenous fistulae.[14,15] Furthermore, a lung structural remodeling may be recognized in CKD patients, mainly characterized by proliferation of fibroblasts with fibrosis and extracellular matrix deposition, resulting in thickening of the alveolar wall.[13] In addition to the uremia-related dysfunction of the pulmonary microcirculation, these mechanisms may cause a restrictive, poorly compliant lung with impaired gas exchange[16]; moreover, the reduction in diffusion capacity for carbon monoxide correlates with the severity of renal impairment in CKD patients.[17] All these mechanisms may 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 for AKI occurrence is increased exponentially. Several mechanisms sustained by organ cross-talk may lead to AKI coming from nonrenal organ damages (Fig. 214.1, Panel B). For example, most

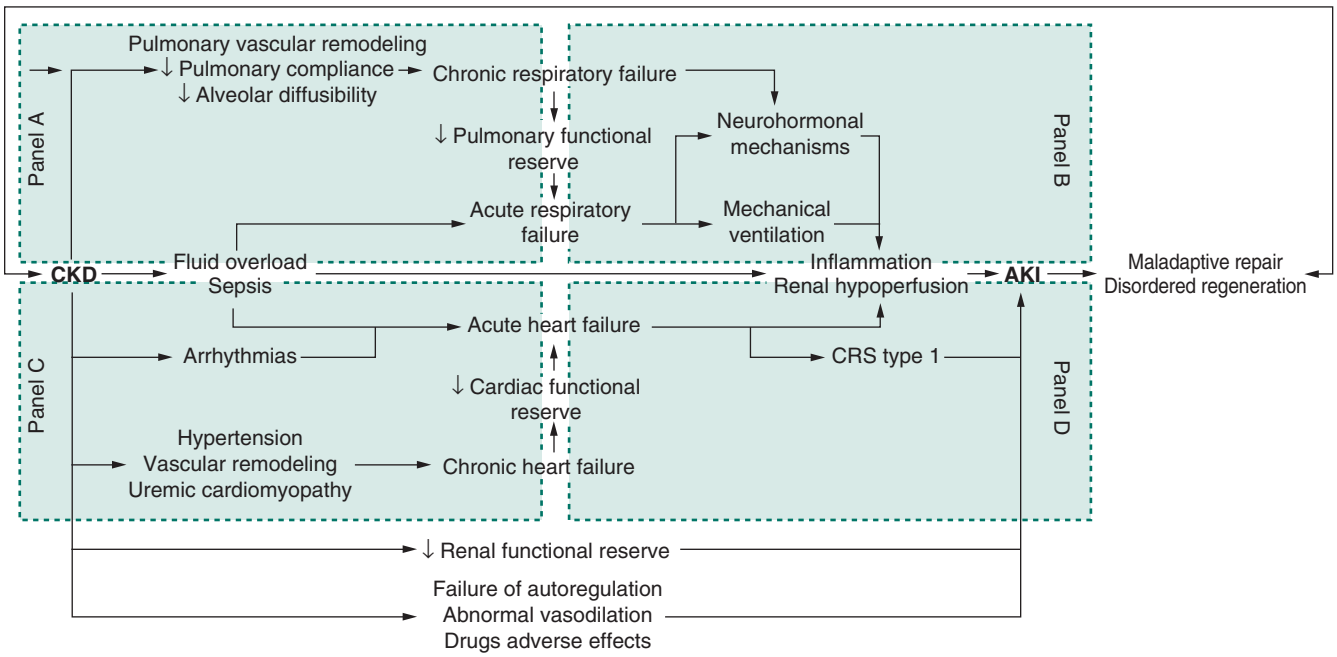


**FIGURE 214.1** Pathophysiologic relationship between chronic kidney disease (CKD) and acute kidney injury (AKI). The maladaptive repair and the disordered regeneration are the principal mechanisms involved in the progression from AKI to advanced stages of CKD. However, most critically ill CKD patients may present a transient decrease in renal function, consistent with AKI. The acute-on-chronic kidney dysfunction may be due to several mechanisms, including failure of autoregulation, abnormal vasodilation, and adverse effects related to diuretics, antihypertensive agents, and/or nephrotoxins, but also the reduction of renal functional reserve.

of patients with respiratory failure admitted in the ICU undergo mechanical ventilation that may have an effect on renal function; the hemodynamic effects of mechanical ventilation potentially leading to kidney hypoperfusion are well established in literature.[18] In particular, positive pressure ventilation may lead to an increase in intrathoracic 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 hypoperfusion. All these hemodynamic effects may occur in patients with an already reduced kidney perfusion, directly related to the cause of respiratory failure (e.g., intraabdominal hypertension[9]), or for the concomitant alteration of neurohormonal pathway (e.g., those aimed at retaining salt and water to maintain an adequate vascular filling pressure to counteract the peripheral vasodilation resulting from hypercapnia). Furthermore, a well-established proinflammatory effect of mechanical ventilation has been associated with an increased susceptibility to develop clinical or subclinical AKI.[19] Indeed, the production of inflammatory mediators, the expression of nitric oxide synthase, the induction of renal epithelial cell apoptosis, and the dysregulation of renal vascular response have been demonstrated to be associated with mechanical ventilation.[19] The more RFR is reduced, the more precocious, severe, and persistent is the kidney damage occurring after all these processes.

Furthermore, CKD has been reported in up to 63% of cases of heart failure.[10] 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.[13] Uremic cardiomyopathy has also a role in the structural and electrophysiologic heart remodeling, leading to biventricular hypertrophy, systolic and diastolic dysfunction, capillary rarefication, and cardiac fibrosis.[20] The AoC uremic pericarditis with sterile effusion is a classical manifestation, although its occurrence is uncommon since the introduction of dialysis.[13] Beyond these mechanisms, several factors may relate the incidence of acute heart failure to CKD (Fig. 214.1, Panel C).

The development of acute heart failure is a pivotal and progressive condition that leads to distant organ damage, because of interorgan cross-talk, whose severity is often proportional to the duration of heart failure. In these conditions, AKI occurs in about 25% to 33% of cases of acute decompensated heart failure (i.e., cardiorenal syndrome type 1 [CRS type 1]),[21] whereas in 60% of them, an AoC kidney dysfunction may be diagnosed.[22] Similarly, for what reported for the lung during respiratory failure, an impairment in cardiomyocytes potentially promotes distant organ damage (i.e., AKI); potential pathophysiologic mechanisms include ischemic and mechanical injury via innate immune system response, neurohormonal signaling, and release of metabolic products (i.e., catalytic iron)[21] (Fig. 214.1, Panel D).

## Acute Kidney Injury Patients Toward Chronic Kidney Disease

The analysis of the pathophysiologic continuum between AKI and CKD also includes the long-term worsening of the kidney function resulting from AKI. Several studies have underlined the incidence, causes, and pathophysiologic mechanisms of CKD/ESKD development after single or repetitive episodes of AKI.[5] These studies have demonstrated consistently that, even when renal function is recovered after the acute insult, most of patients with AKI have a progression to advanced stages of CKD. Interestingly, this progression occurs even in absence of common risk factors (e.g., hypertension, diabetes, or cardiovascular disease[23]), during mild cases, and regardless of the cause of AKI.[5] Although several pathophysiologic mechanisms leading to progression of renal damage in humans have been postulated in literature,[5] the final causal pathways involved to the ongoing organ dysfunction seem to include maladaptive repair, disordered regeneration, or both[24,25] (see Fig. 214.1).

## Chronic Kidney Disease and End-Stage Kidney Disease Patients Admitted in the Intensive Care Unit

Advanced age and higher prevalence of peripheral vascular disease, cerebrovascular disease, ischemic and nonischemic cardiovascular disease, and diabetes mellitus are frequent comorbidities of CKD/ESKD critically ill patients. A recent systematic review demonstrated cardiopulmonary edema and sepsis as the most frequent causes for ICU admission in these patients.[26] Common triggers of cardiopulmonary edema could be represented by pneumonia, excessive interdialytic weight gain, inappropriate prescription, and primary cardiac events.[27] CKD/ESKD is associated with an increased incidence of critical illness and with a greater risk of morbidity and mortality after major surgical procedures.[28]

## Clinical Pictures

### *Cardiovascular Disease*

Sudden death, myocardial infarction, cardiac arrest, and malignant arrhythmias are the major causes of death in CKD/ESKD patients, accounting for 43% of all-cause mortality.[29] CKD/ESKD patients often present left ventricular hypertrophy, arrhythmias resulting from rapid electrolyte shifts during LT-RRT, QT dispersion, sympathetic overactivity, and cardiovascular deposition of calcium phosphate.[29] CKD/ESKD patients with or without residual renal function present a failure of salt and water excretion, which may result in chronic hypertension. Acute pulmonary infection, excessive interdialytic weight gain, inappropriate dry weight prescription, and primary cardiac events are common triggers for acute pulmonary edema.[30] 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.[27] Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T values are less diagnostic in the acute setting in CKD/ESKD patients.[31] Indeed, serum levels of troponin T and NT-proBNP are elevated already in those patients and potentially affected by the modality of LT-RRT, the use of catheter or graft,[32] and high-flux dialyzers that may increase their clearance.

### *Infectious Processes*

After cardiovascular disease, sepsis is the second cause of death in patients with CKD/ESKD.[33] A particular "resistance profile" to antimicrobial therapy can challenge the initial approach, but so can the management, increasing the risk of failure and the costs of care.[34] The high risk of infection is due to attenuated acute inflammatory and immunologic responses,[34,35] such as impairment of phagocytic function.[36] Comorbidities (e.g., diabetes), anatomic abnormalities (e.g., polycystic kidney), and repetitive exposures to nosocomial

microorganisms can increase the risk of sepsis.[37] The most common source of infection is represented by indwelling catheters followed by lower respiratory tract infections,[38] cellulitis, and pyocystis[39,40] 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 early infectious complications,[41] whereas peritoneal dialysis (PD) catheters have a higher rate of late infectious complications, but also higher mortality.[42] *Escherichia coli* and *Staphylococcus epidermidis* are the most common microorganisms.[43] The diagnosis of sepsis is a clinical challenge in CKD/ESKD patients. The sepsis management is based on early goal-directed therapy.[44] 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.[45] However, those patients usually appear to be overloaded and severely hypotensive. For this reason, physicians often regret to perform an aggressive fluid resuscitation causing an underresuscitation and a severe microcirculation impairment. An invasive hemodynamic monitoring and an adequate hydration should be performed associated to fluid removal through early acute RRT (A-RRT). Empiric antibiotics must cover gram-positive (e.g., glycopeptide or cephalosporin) and gram-negative organisms (e.g., third-generation cephalosporin or aminoglycoside),[46] until the isolation of microorganism. Methicillin-resistant *Staphylococcus aureus* (MRSA) cover may be needed if the patient has an indwelling HD or PD catheter.[47] Peritonitis is a significant complication of PD with a mortality of 3.5% to 10%.[48] It is defined by the presence of signs and symptoms, a white cell count in excess of 100 mL of PD effluent, and more than 50% neutrophils after a dwell of at least 2 hours and a positive culture of an organism from the PD effluent.[46] *S. aureus* and *Pseudomonas aeruginosa* are the most common organisms implicated in peritonitis of PD.

## Major Surgical Procedures

Data on the possible impact of CKD/ESKD on outcome after major surgical procedures are scarce. For this reason it is not possible to perform a risk stratification of surgical patients. Patients with residual renal function before surgery and postoperative anuria have higher mortality rates 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.[49] In addition, perioperative hemodynamic status and biochemical factors are also related to patient's mortality.[50]

## Management

In intensive care environment, the A-RRT prescription and management for CKD/ESKD patient depend on several factors, such as modality and access of preexisting 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.[51]

The target point of management (Table 214.1) is represented by the following sections.

**TABLE 214.1**

**Management of End-Stage Kidney Disease Patients in the Intensive Care Unit**

| | |
|---|---|
| Volume status control | • Administer isotonic fluids to maintain a normal serum sodium concentration and tonicity<br>• Perform a daily assessment of weight, fluid intake, and output<br>• Monitor central venous pressure and central venous oxygen saturation<br>• Perform hemodynamic invasive monitoring |
| Electrolyte control | • Consider insulin and salbutamol to treat hyperkalemia and initiate A-RRT promptly<br>• Avoid hypokalemia during RRT because of risk of cardiac arrhythmias<br>• Hypotonic hyponatremia, hyperphosphatemia, and hypocalcemia are frequent<br>• Hypercalcemia may be a consequence of excessive calcium supplementation or related to the underlying cause of renal failure |
| Dialysis access and vein preservation | • Consider absolute and relative indication to PD catheters use<br>• Avoid arteriovenous fistulas and grafts for CRRT, but consider it for IHD or hybrid therapies in ICU, if necessary<br>• Avoid placing identification bands or restraints over the fistula<br>• An internal jugular line for short-term or tunneled access is recommended<br>• Minimize venipuncture, limit placement of peripherally inserted central catheter (PICC), and avoid use of subclavian venous site |
| Hemostasis | • Bleeding diatheses are frequent because of platelets dysfunction and extracorporeal therapies<br>• Low-molecular-weight heparin to maintain patency of the extracorporeal dialysis circuit is of similar efficacy and safety to unfractionated heparin<br>• Sodium citrate may be used for "regional anticoagulation," where systemic anticoagulation is undesirable<br>• 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 | • Consider reduced GFR, the altered protein binding, the variable volume of distribution, and the RRT mode when prescribing a drug<br>• The required dose of propofol should be titrated to effect, and it is better to avoid continuous infusion of midazolam<br>• Morphine and fentanyl accumulate in renal failure, and they should be used with caution; remifentanil has no toxic effect<br>• 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<br>• Avoid undertreatment and adverse effects but also consider pharmacokinetic/pharmacodynamic and extracorporeal clearance when prescribing an antibiotic |

## Volume Status Control

The volume management in CKD/ESKD patients with sepsis, acute respiratory distress syndrome (ARDS), 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 is preferable to maintain a normal serum sodium concentration and tonicity. In addition, hypotonic infusions (e.g., vasopressors) and certain antibiotics administrated in 5% dextrose should be predicted.[51] It is important to assess weight, fluid intake, and output daily as well as monitor central venous pressure, central venous oxygen saturation, and if possible perform hemodynamic invasive monitoring. Noninvasive methods such as bioimpedance[52–55] and ultrasonography techniques[56,57] have demonstrated their diagnostic value in CKD/ESKD and critically ill patients.

## Electrolyte Control

CKD/ESKD patients, because of limited capacity to maintain homeostatic control, present disorders of potassium, sodium, calcium, magnesium, and phosphate. The overadministration the reduced excretion, or the leakage from intracellular pools may prompt the development of life-threatening hyperkalemia with the need for pharmacologic and/or dialytic intervention.[58] Combination treatment of hyperkalemia with insulin and salbutamol is synergistic and safe in patients with CKD/ESKD.[59] In addition, treatment with A-RRT must be instituted promptly. If A-RRT is delayed, the ESKD patient may experience "rebound hyperkalemia" because the potassium ions return to the extracellular space but are not excreted by the kidneys. Conversely, hypokalemia during RRT should be avoided because of the risk of cardiac arrhythmia, and careful monitoring of potassium should be advocated.[60] The loss of the ability to excrete a free-water load predisposes to development of moderate-to-severe hypotonic hyponatremia. Such patients are also susceptible to the development of hyperphosphatemia and hypocalcemia related to disorders in calcium-phosphate metabolism. In addition, the use of citrate anticoagulation for RRT may exacerbate underlying hypocalcemia because of chelation of serum calcium.[61] On the contrary, hypercalcemia may be a consequence of excessive calcium supplementation or related to the underlying cause of renal failure such as multiple myeloma.

## Dialysis Access and Vein Preservation

**PERITONEAL DIALYSIS CATHETERS.** Sepsis represents an absolute contraindication for PD use. On the contrary, the presence of intraabdominal foreign bodies, peritoneal leaks, inflammatory or ischemic bowel disease, abdominal wall or skin infection, and severe malnutrition are relative contraindications to performing PD.[62] Thus the use of a PD catheter after an ICU admission generally is reduced.

**ARTERIOVENOUS 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. Similarly, bands or restraints over the fistula should be avoided. Arteriovenous fistula may 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 resulting from infection, thrombosis, and/or stenosis of previous catheters. An internal jugular line for short-term or tunneled access is recommended.[63]

**VEIN PRESERVATION.** Minimizing venipuncture and limiting placement of peripheral inserted central catheter (PICC) 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

Patients with CKD/ESKD exhibit a slightly different pattern of coagulopathies than the general population. CKD/ESKD patients develop hemostatic disorders mainly in the form of bleeding diatheses from hemorrhage of cutaneous sites until to retroperitoneal or intracranial hemorrhages. Platelets dysfunction (impaired adhesion and decreased aggregation) is the main responsible factor. Extracorporeal therapies (IHD, hybrid therapies, and CRRT), which are able to partially correct those defects, can contribute to the bleeding too. HD also is associated to thrombosis because of chronic platelet activation because of the contact with artificial surfaces during dialysis.[64] The use of low-molecular-weight heparin to maintain patency of the extracorporeal dialysis circuit is of similar efficacy and safety to 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.[65] 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.[64]

## Imaging

Performing HD immediately after iodinated contrast administration does not reduce the risk of AKI.[66] Iodinated contrast represents a combined vasoconstrictive 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 the vast majority of patients with ESKD, who are dialyzed adequately, there is no need to perform HD immediately after radiocontrast administration.[67]

## 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, whereas the hemodilution or the albumin adsorption could decrease its plasma concentrations.[68] For this reason, the required dose of propofol should be titrated to effect. Midazolam is metabolized from the liver to its active metabolite, a1-hydroxymidazolam. During a renal impairment, the elimination of a1-hydroxymidazolam and the protein binding of midazolam is reduced.[69] The removal of midazolam through CRRT is not efficient. Bolus

doses of midazolam therefore should be reduced and titrated according to the effect in CKD/ESKD patients. In addition, the use of midazolam infusions in critically ill patients with ESKD should 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 accumulate in renal failure.[70] A minimal amount of morphine could be removed during hemofiltration or hemodiafiltration, whereas a significant quantity of free morphine may be removed in hemodialysis because of a much higher dialysate flow rate.[71] Although the use of fentanyl is often preferred in patients with renal impairment,[72] the dose reduction is necessary because the accumulation will result in toxicity.[73] Moreover, fentanyl is not cleared by hemodialysis. Remifentanil clearance is clinically independent of renal function, but its metabolite, remifentanil acid, accumulates in renal failure without a toxic effect.[74]

**DIURETICS.** Diuretics are limited for CKD patients 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). Moreover, in ICU setting, malnourishment and transcapillary leak may lead to hypoalbuminemia and an increase in distribution volume that further worsens diuretic resistance. Therefore in critically ill CKD patients, diuretics dose should be increased progressively 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.[75]

**ANTIBIOTICS.** Drug dosage adjustment should take into consideration the peculiar pharmacokinetic/pharmacodynamic characteristics of critically ill patients but also the superimposed extracorporeal clearance resulting from A-RRT (e.g., dose, modality).[51] The issue of antimicrobial adjustment should be considered in those critically ill CKD/ESKD patients to avoid undertreatment (and thus eradication failure and antimicrobial resistance occurrence) and adverse effects (e.g., nephrotoxins for several antibiotics).

## TRANSITION FROM INTERMITTENT HEMODIALYSIS OR PERITONEAL DIALYSIS TO CONTINUOUS RENAL REPLACEMENT THERAPY

Despite the fact that kidney transplantation is now considered the optimal treatment for most ESKD patients[76,77] and conservative care has been demonstrated to have more or similar advantages in frail elderly patients,[78] 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.[79,80] When an ESKD patient is admitted in the ICU, the most beneficial and appropriate RRT modality should be selected. Unfortunately, the decision is due to not only patient's need but also to organizational characteristics, such as availability of technologic and human resources and expertise of staff. CRRT is the predominant RRT modality used in Australia and in most European countries, and its use in the United States is increasing.[81–84] Considerations about clinical conditions requiring CRRT in ESKD patients do not differ from 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. 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.[85] The use of PD in ICU unstable patients, despite 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.

The other specific situation in which the transition from IHD to CRRT is mandatory is the occurrence of intracranial hypertension and/or acute brain injury.[63] In fact, IHD has been associated with further increases in intracranial pressure.[86] In addition, CRRT has been demonstrated superior to PD to avoid hyponatremia and thermal losses.[87]

In more recent years, hybrid therapies, such as sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD), and prolonged intermittent RRT (PIRRT) have developed. They seem to be 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 theoretic advantages and the promising results, the precise role of hybrid techniques should be investigated further with randomized controlled trials (RCT).[88,89]

Finally, in clinical settings in which blood purification requirement is accompanied by multiple organ failure or septic shock, CRRT is recommended.[90]

When the RRT modality has been selected, an individualization of nutrition as well as a dose adjustment of prescribed drugs (i.e., antibiotics, antifungal agents) should be taken into account.[63] Despite there are no available recommendations to modify drugs dose in a given patient with a given RRT modality, a deep knowledge of dialysis techniques and kinetic of different drugs may drive clinicians to prescribe the adequate drug dosage and dosing intervals.[91,92] Moreover, monitoring the plasma level of drugs, when available, may help to individualize therapy further, avoiding under- or overdosing.

## TRANSITION FROM CONTINUOUS RENAL REPLACEMENT THERAPY TO INTERMITTENT HEMODIALYSIS OR PERITONEAL DIALYSIS

In hemodynamically stable patients, studies failed to demonstrate the superiority of one RRT modality over the others, whereas CRRT and IHD are shown to guarantee an adequate metabolic control.[85,93,94] 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.[90]

When the critical illness has been solved, patients who were on maintenance IHD or PD before the ICU admission can restart their previous therapy progressively. 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 recover renal function and require chronic RRT should be addressed to a dialysis modality (IHD or PD) according to patients' clinical and individual needs.

In transition from CRRT to intermittent RRT, the same considerations discussed above about nutrition and drug dose should be taken into account.

## RECOVERY FROM ACUTE KIDNEY INJURY AND RISK TO DEVELOP CHRONIC KIDNEY DISEASE

Once the acute kidney insult has been solved, renal function may be fully, partially, or not recovered, and various degrees of CKD, until ESKD requiring maintenance RRT, may persist. The exact rate as well as the pathophysiologic pathways of progression to CKD are still under investigation.[95] Despite there are some evidences that patients initially treated with CRRT have a lower rate of ESKD requiring maintenance RRT,[96,97] a recent large single-center retrospective study found no difference in renal recovery rate between CRRT and IHD as initial RRT modality.[98] Discontinuation of RRT should be taken into account when renal recovery is enough to allow a sufficient metabolic, electrolyte, and fluid balance.[90] The right timing is unknown and some markers have been proposed to drive RRT weaning. The most used clinical criteria are serum creatinine (SCr) levels with a constant dialysis dose and urine output.[99] Recently, daily urinary urea excretion [24 hours-Urinary Urea, 24h-UU] and daily urinary creatinine excretion [24 hours-Urinary Creatinine, 24h-UCr] have been evaluated in two different single-center retrospective studies. Both have been demonstrated to be superior to other markers and 24h-UCr than 24h-UU in predicting RRT weaning success.[100,101]

## CONCLUSION

There are a large number of subjects who clinically manifest CKD at the moment of ICU admission. In the wide spectrum of CKD, however, we must consider also subclinical forms of renal insufficiency (reduction of renal functional reserve) and, in the other extreme, patients already on ESKD and chronic dialysis treatment.

These patients suffer from increased risk of complications resulting from the important comorbidity carried by the effect of chronic kidney dysfunction. Some of these patients present with a worsening of renal function that should be defined as AoC.

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 require a multidisciplinary approach to the 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 complex patients and should implement a common strategy to minimize complications and negative short- and long-term outcomes.

### Key Points

1. The relationship among AKI, CKD, and ESKD is highly complex. 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. If the acute insult, which led to AKI, occurs in CKD patients, a maladaptive repair may accelerate the progression of CKD patients toward ESKD.
2. Cardiopulmonary edema and sepsis as the most frequent causes for ICU admission of ESKD patients. The management for CKD/ESKD patient depend on several factors, such as modality and access of preexisting LT-RRT, hemodynamic status, physician and staff experience, and ICU resources.
3. A multidisciplinary approach but also preventive and protective strategies are required to avoid further AKI episodes. 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.

## Key References

1. Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS ONE*. 2016;11:e0158765.
5. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371:58-66.
26. Arulkumaran N, Annear NM, Singer M. Patients with end-stage renal disease admitted to the intensive care unit: systematic review. *Br J Anaesth*. 2013;110:13-20.
90. Ostermann M, Joannidis M, Pani A, et al. Patient selection and timing of continuous renal replacement therapy. *Blood Purif*. 2016;42:224-237.
102. De Rosa S, Samoni S, Villa G, et al. Management of chronic kidney disease patients in the intensive care unit. Mixing acute and chronic illness. Blood Purif (in press).

A complete reference list can be found online at ExpertConsult.com.

## References


1. Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS ONE*. 2016;11:e0158765.
2. Murphy D, McCulloch CE, Lin F, et al. Trends in prevalence of chronic kidney disease in the united states. *Ann Intern Med*. 2016;165(7):473-481.
3. Rimes-Stigare C, Frumento P, Bottai M, et al. Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease. *Crit Care*. 2015;19:383.
4. Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ*. 2013;346:f324.
5. Chawla LS, Eggers PW, Star RA, et al. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371:58-66.
6. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*. 2009;20:223-228.
7. Xue JL, Daniels F, Star RA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J Am Soc Nephrol*. 2006;17:1135-1142.
8. Sharma A, Mucino MJ, Ronco C. Renal functional reserve and renal recovery after acute kidney injury. *Nephron Clin Pract*. 2014;127:94-100.
9. Villa G, Samoni S, De Rosa S, et al. The pathophysiological hypothesis of kidney damage during intra-abdominal hypertension. *Front Physiol*. 2016;7:55.
10. Sharma A, Zaragoza JJ, Villa G, et al. Optimizing a kidney stress test to evaluate renal functional reserve. *Clin Nephrol*. 2016;86:18-26.
11. Samoni S, Nalesso F, Meola M, et al. Intra-parenchymal renal resistive index variation (IRRIV) describes renal functional reserve (RFR): pilot study in healthy volunteers. *Front Physiol*. 2016;7:286.
12. Bosch JP, Lauer A, Glabman S. Short-term protein loading in assessment of patients with renal disease. *Am J Med*. 1984;77:873-879.
13. Husain-Syed F, McCullough PA, Birk HW, et al. Cardiopulmonary-renal interactions: a multidisciplinary approach. *J Am Coll Cardiol*. 2015;65:2433-2448.
14. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62:D34-D41.
15. Pabst S, Hammerstingl C, Hundt F, et al. Pulmonary hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study. *PLoS ONE*. 2012;7:e35310.
16. Ewert R, Opitz C, Wensel R, et al. Abnormalities of pulmonary diffusion capacity in long-term survivors after kidney transplantation. *Chest*. 2002;122:639-644.
17. Moinard J, Guenard H. Membrane diffusion of the lungs in patients with chronic renal failure. *Eur Respir J*. 1993;6:225-230.
18. Husain-Syed F, Slutsky AS, Ronco C. Lung-kidney cross-talk in the critically ill patient. *Am J Respir Crit Care Med*. 2016;194:402-414.
19. Koyner JL, Murray PT. Mechanical ventilation and the kidney. *Blood Purif*. 2010;29:52-68.
20. Gross ML, Ritz E. Hypertrophy and fibrosis in the cardiomyopathy of uremia–beyond coronary heart disease. *Semin Dial*. 2008;21:308-318.
21. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol*. 2012;60:1031-1042.
22. Cruz DN, Bagshaw SM. Heart-kidney interaction: epidemiology of cardiorenal syndromes. *Int J Nephrol*. 2010;2011:351291.
23. Goldstein SL. Acute kidney injury in children and its potential consequences in adulthood. *Blood Purif*. 2012;33:131-137.
24. Venkatachalam MA, Griffin KA, Lan R, et al. Acute kidney injury: a springboard for progression in chronic kidney disease. *Am J Physiol Renal Physiol*. 2010;298:F1078-F1094.
25. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int*. 2012;82:516-524.
26. Arulkumaran N, Annear NM, Singer M. Patients with end-stage renal disease admitted to the intensive care unit: systematic review. *Br J Anaesth*. 2013;110:13-20.
27. Halle MP, Hertig A, Kengne AP, et al. Acute pulmonary oedema in chronic dialysis patients admitted into an intensive care unit. *Nephrol Dial Transplant*. 2012;27:603-607.
28. Apel M, Maia VP, Zeidan M, et al. End-stage renal disease and outcome in a surgical intensive care unit. *Crit Care*. 2013;17:R298.
29. Kanbay M, Solak Y, Covic A, et al. Sudden cardiac death in patients with chronic kidney disease: prevention is the sine qua non. *Kidney Blood Press Res*. 2011;34:269-276.
30. Zoccali C, Mallamaci F, Tripepi G. Hypertension as a cardiovascular risk factor in end-stage renal failure. *Curr Hypertens Rep*. 2002;4:381-386.
31. Sommerer C, Beimler J, Schwenger V, et al. Cardiac biomarkers and survival in haemodialysis patients. *Eur J Clin Invest*. 2007;37:350-356.
32. Sommerer C, Heckele S, Schwenger V, et al. Cardiac biomarkers are influenced by dialysis characteristics. *Clin Nephrol*. 2007;68:392-400.
33. Collins AJ, Foley RN, Chavers B, et al. US Renal Data System 2013 Annual Data Report. *Am J Kidney Dis*. 2014;63:A7.
34. Pop-Vicas A, Strom J, Stanley K, et al. Multidrug-resistant gram-negative bacteria among patients who require chronic hemodialysis. *Clin J Am Soc Nephrol*. 2008;3:752-758.
35. Pesanti EL. Immunologic defects and vaccination in patients with chronic renal failure. *Infect Dis Clin North Am*. 2001;15:813-832.
36. Vanholder R, Ringoir S. Polymorphonuclear cell function and infection in dialysis. *Kidney Int Suppl*. 1992;38:S91-S95.
37. Wang HE, Gamboa C, Warnock DG, et al. Chronic kidney disease and risk of death from infection. *Am J Nephrol*. 2011;34:330-336.
38. Powe NR, Jaar B, Furth SL, et al. Septicemia in dialysis patients: incidence, risk factors, and prognosis. *Kidney Int*. 1999;55:1081-1090.
39. Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA*. 2016;316:325-337.
40. Stafford P, Prybys KM. Pyocystis and prostate abscess in a hemodialysis patient in the emergency department. *West J Emerg Med*. 2014;15:655-658.
41. Aslam N, Bernardini J, Fried L, et al. Comparison of infectious complications between incident hemodialysis and peritoneal dialysis patients. *Clin J Am Soc Nephrol*. 2006;1:1226-1233.
42. Johnson DW, Dent H, Hawley CM, et al. Associations of dialysis modality and infectious mortality in incident dialysis patients in Australia and New Zealand. *Am J Kidney Dis*. 2009;53:290-297.
43. Abou Dagher G, Harmouche E, Jabbour E, et al. Sepsis in hemodialysis patients. *BMC Emerg Med*. 2015;15:30.
44. Cho WH. Update of sepsis: recent evidences about early goal directed therapy. *Tuberc Respir Dis (Seoul)*. 2015;78:156-160.
45. Otero RM, Nguyen HB, Huang DT, et al. Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. *Chest*. 2006;130:1579-1595.
46. Li PK, Szeto CC, Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int*. 2010;30:393-423.
47. Fluck R, Wilson J, Davies J, et al. UK Renal Registry 11th Annual Report (December 2008): Chapter 12 Epidemiology of methicillin resistant Staphylococcus aureus bacteraemia amongst patients receiving renal replacement therapy in England in 2007. *Nephron Clin Pract*. 2009;111(suppl 1):c247-c256.
48. Mujais S. Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl*. 2006;S55-S62.
49. Lin YF, Wu VC, Ko WJ, et al. Residual urine output and postoperative mortality in maintenance hemodialysis patients. *Am J Crit Care*. 2009;18:446-455.

50. Cooper WA, O'Brien SM, Thourani VH, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation*. 2006;113:1063-1070.
51. Szamosfalvi B, Yee J. Considerations in the critically ill ESRD patient. *Adv Chronic Kidney Dis*. 2013;20:102-109.
52. Pillon L, Piccoli A, Lowrie EG, et al. Vector length as a proxy for the adequacy of ultrafiltration in hemodialysis. *Kidney Int*. 2004;66:1266-1271.
53. Piccoli A. Bioelectric impedance vector distribution in peritoneal dialysis patients with different hydration status. *Kidney Int*. 2004;65:1050-1063.
54. Samoni S, Vigo V, Resendiz LI, et al. Impact of hyperhydration on the mortality risk in critically ill patients admitted in intensive care units: comparison between bioelectrical impedance vector analysis and cumulative fluid balance recording. *Crit Care*. 2016;20:95.
55. Jones SL, Tanaka A, Eastwood GM, et al. Bioelectrical impedance vector analysis in critically ill patients: a prospective, clinician-blinded investigation. *Crit Care*. 2015;19:290.
56. Basso F, Milan Manani S, Cruz DN, et al. Comparison and reproducibility of techniques for fluid status assessment in chronic hemodialysis patients. *Cardiorenal Med*. 2013;3:104-112.
57. Zhang Z, Xu X, Ye S, et al. Ultrasonographic measurement of the respiratory variation in the inferior vena cava diameter is predictive of fluid responsiveness in critically ill patients: systematic review and meta-analysis. *Ultrasound Med Biol*. 2014;40:845-853.
58. Evans K, Reddan DN, Szczech LA. Nondialytic management of hyperkalemia and pulmonary edema among end-stage renal disease patients: an evaluation of the evidence. *Semin Dial*. 2004;17:22-29.
59. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int*. 1990;38:869-872.
60. Musso CG. Potassium metabolism in patients with chronic kidney disease. Part II: patients on dialysis (stage 5). *Int Urol Nephrol*. 2004;36:469-472.
61. Brain M, Parkes S, Fowler P, et al. Calcium flux in continuous venovenous haemodiafiltration with heparin and citrate anticoagulation. *Crit Care Resusc*. 2011;13:72-81.
62. Akoh JA. Peritoneal dialysis associated infections: an update on diagnosis and management. *World J Nephrol*. 2012;1:106-122.
63. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120:c179-c184.
64. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. *Semin Dial*. 2006;19:317-322.
65. Kutsogiannis DJ, Gibney RT, Stollery D, et al. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney Int*. 2005;67:2361-2367.
66. Cruz DN, Goh CY, Marenzi G, et al. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Med*. 2012;125:66-78 e63.
67. Weisbord SD, Palevsky PM. Iodinated contrast media and the role of renal replacement therapy. *Adv Chronic Kidney Dis*. 2011;18:199-206.
68. Eddleston JM, Pollard BJ, Blades JF, et al. The use of propofol for sedation of critically ill patients undergoing haemodiafiltration. *Intensive Care Med*. 1995;21:342-347.
69. Driessen JJ, Vree TB, Guelen PJ. The effects of acute changes in renal function on the pharmacokinetics of midazolam during long-term infusion in ICU patients. *Acta Anaesthesiol Belg*. 1991;42:149-155.
70. Osborne R, Joel S, Grebenik K, et al. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther*. 1993;54:158-167.
71. Jamal JA, Joh J, Bastani B. Removal of morphine with the new high-efficiency and high-flux membranes during haemofiltration and haemodialfiltration. *Nephrol Dial Transplant*. 1998;13:1535-1537.
72. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage*. 2004;28:497-504.
73. Koehntop DE, Rodman JH. Fentanyl pharmacokinetics in patients undergoing renal transplantation. *Pharmacotherapy*. 1997;17:746-752.
74. Hoke JF, Shlugman D, Dershwitz M, et al. Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers. *Anesthesiology*. 1997;87:533-541.
75. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol*. 2002;13:798-805.
76. Abecassis M, Bartlett ST, Collins AJ, et al. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. *Clin J Am Soc Nephrol*. 2008;3:471-480.
77. Knoll GA. Is kidney transplantation for everyone? The example of the older dialysis patient. *Clin J Am Soc Nephrol*. 2009;4:2040-2044.
78. O'Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. *J Palliat Med*. 2012;15:228-235.
79. Hutchison CA, Crowe AV, Stevens PE, et al. Case mix, outcome and activity for patients admitted to intensive care units requiring chronic renal dialysis: a secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care*. 2007;11:R50.
80. Strijack B, Mojica J, Sood M, et al. Outcomes of chronic dialysis patients admitted to the intensive care unit. *J Am Soc Nephrol*. 2009;20:2441-2447.
81. Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. *Crit Care Resusc*. 2008;10:225-230.
82. Mehta RL, Letteri JM. Current status of renal replacement therapy for acute renal failure. A survey of US nephrologists. The National Kidney Foundation Council on Dialysis. *Am J Nephrol*. 1999;19:377-382.
83. Legrand M, Darmon M, Joannidis M, et al. Management of renal replacement therapy in ICU patients: an international survey. *Intensive Care Med*. 2013;39:101-108.
84. Bellomo R, Ronco C. Blood purification in the intensive care unit: evolving concepts. *World J Surg*. 2001;25:677-683.
85. Rabindranath K, Adams J, Macleod AM, et al. Intermittent versus continuous renal replacement therapy for acute renal failure in adults. *Cochrane Database Syst Rev*. 2007;(3):CD003773.
86. Ronco C, Bellomo R, Brendolan A, et al. Brain density changes during renal replacement in critically ill patients with acute renal failure. Continuous hemofiltration versus intermittent hemodialysis. *J Nephrol*. 1999;12:173-178.
87. Davenport A. Management of acute kidney injury in neurotrauma. *Hemodial Int*. 2010;14(suppl 1):S27-S31.
88. Zhang L, Yang J, Eastwood GM, et al. Extended daily dialysis versus continuous renal replacement therapy for acute kidney injury: a meta-analysis. *Am J Kidney Dis*. 2015;66:322-330.
89. Neves JB, Rodrigues FB, Castelao M, et al. Extended daily dialysis versus intermittent hemodialysis for acute kidney injury: a systematic review. *J Crit Care*. 2016;33:271-273.
90. Ostermann M, Joannidis M, Pani A, et al. Patient selection and timing of continuous renal replacement therapy. *Blood Purif*. 2016;42:224-237.
91. Schetz M. Drug dosing in continuous renal replacement therapy: general rules. *Curr Opin Crit Care*. 2007;13:645-651.
92. Kuang D, Verbine A, Ronco C. Pharmacokinetics and antimicrobial dosing adjustment in critically ill patients during continuous renal replacement therapy. *Clin Nephrol*. 2007;67:267-284.
93. Pannu N, Klarenbach S, Wiebe N, et al. Renal replacement therapy in patients with acute renal failure: a systematic review. *JAMA*. 2008;299:793-805.
94. Bagshaw SM, Berthiaume LR, Delaney A, et al. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Crit Care Med*. 2008;36:610-617.
95. Zager RA. Progression from acute kidney injury to chronic kidney disease: clinical and experimental insights and queries. *Nephron Clin Pract*. 2014;127:46-50.

96. Schneider AG, Bellomo R, Bagshaw SM, et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med*. 2013;39:987-997.
97. Wald R, Shariff SZ, Adhikari NK, et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study. *Crit Care Med*. 2014;42: 868-877.
98. Liang KV, Sileanu FE, Clermont G, et al. Modality of RRT and recovery of kidney function after AKI in patients surviving to hospital discharge. *Clin J Am Soc Nephrol*. 2016;11: 30-38.
99. Uchino S, Bellomo R, Morimatsu H, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Crit Care Med*. 2009;37:2576-2582.
100. Aniort J, Ait Hssain A, Pereira B, et al. Daily urinary urea excretion to guide intermittent hemodialysis weaning in critically ill patients. *Crit Care*. 2016;20:43.
101. Viallet N, Brunot V, Kuster N, et al. Daily urinary creatinine predicts the weaning of renal replacement therapy in ICU acute kidney injury patients. *Ann Intensive Care*. 2016;6:71.
102. De Rosa S, Samoni S, Villa G, et al. Management of chronic kidney disease patients in the intensive care unit. Mixing acute and chronic illness. Blood Purif (in press).