CHAPTER 14

Acute Kidney Injury in Patients With Chronic Kidney Disease

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OBJECTIVES

This chapter will:

1. Describe the pathophysiologic mechanisms underlying the development of acute-on-chronic kidney dysfunction among chronic kidney disease (CKD) patients and its role in the progression toward end-stage renal disease (ESRD).
2. Detail the most common clinical presentations of critical illness among CKD and ESRD patients.
3. Address the continuum of care necessary for CKD and ESRD patients developing critical illness.

Over the last 20 years the incidence of chronic kidney disease (CKD) has risen[1,2] progressively, reflecting an aging population living with a greater burden of comorbid disease. These trends have resulted in a progressive increase in the proportion of patients with significant preexisting renal dysfunction and ESRD in those presenting to the intensive care unit (ICU) with acute critical illness.[3] As these trends also have been accompanied by an increased availability of ICU beds and willingness to admit patients with chronic disease to the ICU, the management of "critically ill CKD patients" has now become routine clinical challenge for nephrologists and intensivists. However, several epidemiologic studies have shown that preexisting renal dysfunction is associated with significantly increased risk of death during critical illness, highlighting the important of careful assessment and management of these patients.[4]

The development of acute-on-chronic kidney disease, that is, acute kidney injury (AKI) occurring in a patient with CKD during acute illness, is common and is associated with short-term risk of death and, in survivors, accelerated progression of CKD culminating in the development of ESRD.[3] Despite this interrelationship between AKI, CKD, and ESRD, nephrologists and intensivists historically have classified the acute and chronic renal dysfunction as two separate clinical syndromes, a conceptual approach that, although convenient, ignores many common elements in the pathophysiology.[5] Specifically, CKD is among the strongest risk factors for development of AKI during acute illness, whereas episodes of AKI are a major mechanism behind the development and progression of CKD.[5] As a result of this common pathophysiology, individuals may develop a vicious cycle of recurrent AKI and an accelerating stepwise deterioration of underlying CKD, resulting in either ESRD or causes of death predisposed by advanced chronic kidney disease or a recurrent episode of AKI (Fig. 14.1).

Thus, given high prevalence rate of CKD, its associated increased risk of morbidity and mortality during critical illness, and the association with adverse long-term outcomes after ICU, an integrated multidisciplinary approach to these patients is advocated. In particular, prevention, early recognition, and management of AKI is essential to limit the progression of chronic kidney dysfunction during critically illness.[3]

CHRONIC KIDNEY DISEASE AND THE DEVELOPMENT OF ACUTE KIDNEY INJURY

Preexisting CKD is associated with a more than tenfold risk for AKI development during acute illness[6,7] and critical illness in particular[3] and is the strongest identifiable risk factor for the development of AKI in these settings. Multiple factors underlie this propensity to acute-on-chronic renal dysfunction, including impaired autoregulation of renal blood flow, endothelial dysfunction, and the adverse effect of concomitant medications, including diuretics, antihypertensive agents, and other potential nephrotoxins[5] (Fig. 14.2). Furthermore, the coexistence of nonrenal chronic organ dysfunction associated with CKD such as diastolic heart dysfunction and systemic vascular calcification may predispose to AKI in the context of acute illness as a result of inadequate cardiovascular and respiratory reserve to respond to acute illness. Finally, even in apparently mild CKD, loss of nephron mass and reduction of renal functional reserve (RFR) may increase the vulnerability of CKD patients for the development of AKI,[8] particularly if baseline GFR is maintained by a degree of glomerular hyperfiltration as is common in early diabetic nephropathy, for instance. RFR is the amount of recruitable renal clearance capability available to meet an acute metabolic stress.[9] It can be quantified as the capacity to increase glomerular filtration rate (GFR) with an acute demand such as a protein load.[10,11] RFR is reduced progressively with worsening CKD[12]; the susceptibility of each CKD patient to develop

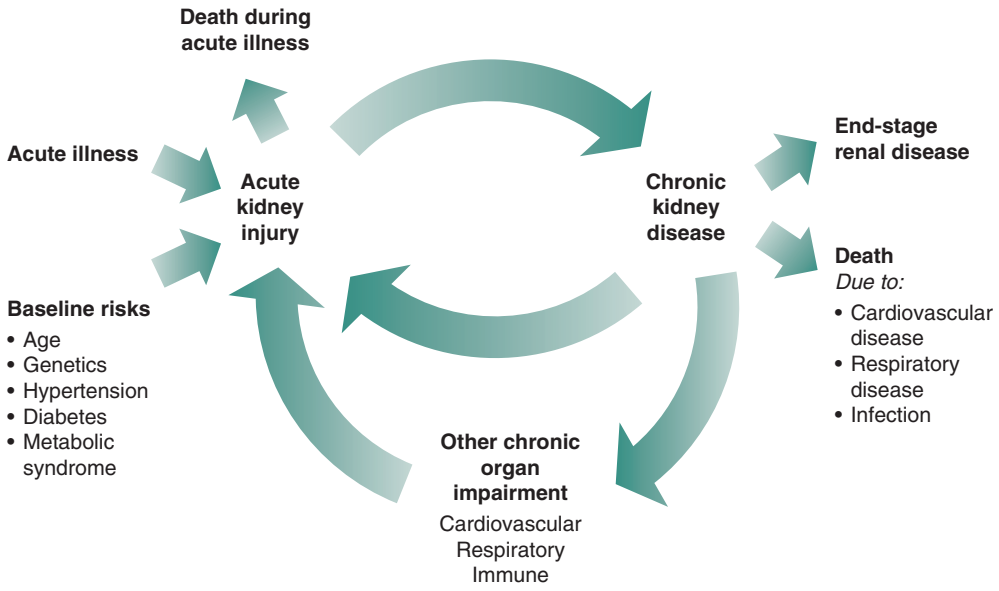

FIGURE 14.1 The relationship between acute kidney injury (AKI) and chronic kidney disease (CKD) can give rise to a vicious cycle of recurrent AKI and worsening CKD culminating in either death during acute illness, death from chronic disease, (particularly cardiovascular disease) or the development of end-stage renal disease.

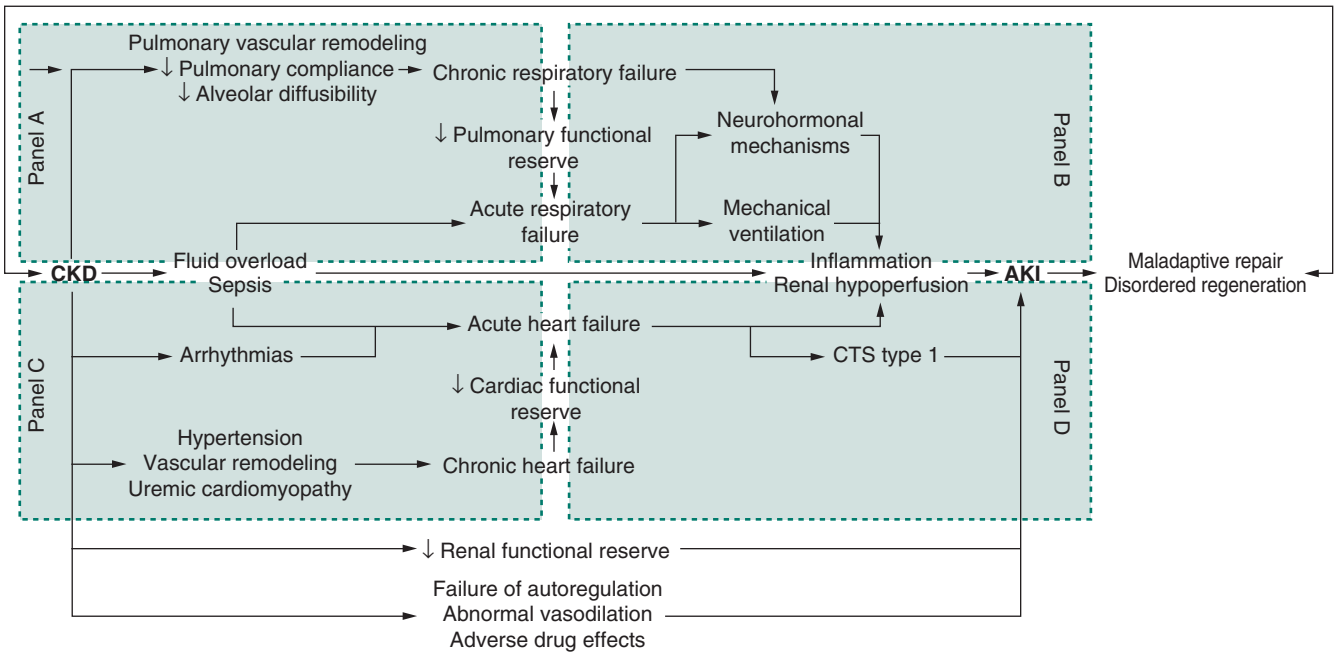

FIGURE 14.2 Pathophysiologic relationship between chronic kidney disease (CKD), acute kidney injury (AKI), and other organ dysfunctions. Acute-on-chronic kidney dysfunction can arise from several mechanisms, including cardiac or respiratory failure, failure of renal autoregulation, endothelial dysfunction and drugs, and underlying reduction of RFR exposed by the increased demand of critical illness. *Panel A,* CKD is associated with acute and chronic respiratory failure. *Panel B,* Acute respiratory failure is associated with development of AKI. *Panel C,* CKD is associated with acute and chronic cardiac disease. *Panel D,* Cardiac failure is associated with development of AKI. Maladaptive repair and the disordered regeneration are the principal mechanisms involved in the progression from AKI to worsened CKD closing the loop of progression of CKD progression.

AKI is directly proportional to the degree of RFR reduction[9] (see Fig. 14.2).

As well as increased risk of AKI, CKD predisposes to other acute organ dysfunctions during critical illness, particularly to cardiac and pulmonary dysfunction.[13] CKD patients are at particular risk of acute respiratory failure complicating critical illness (see Fig. 14.2A), as well as susceptible to fluid overload and impaired immunity leading to the development of sepsis. A number of specific pathophysiologic mechanisms may explain the high incidence of acute respiratory failure in patients with CKD and intercurrent illness. For example, CKD is associated with

the development of pulmonary hypertension[14] through a number of mechanisms, including fluid overload, endothelial dysfunction, decreased bioavailability of nitric oxide, increased circulating levels of endothelin-1, and pulmonary vascular remodeling.[15] Similarly, structural lung remodeling is observed in patients with CKD characterized by alveolar wall fibrosis and extracellular matrix deposition,[13] causing a degree of convert fibrotic lung disease predisposing to respiratory failure.[16] In support of this mechanism, reduced diffusion capacity for carbon monoxide has been shown to correlate with severity of renal impairment in CKD patients.[17]

Development of other organ failure then may predispose itself to the occurrence or worsening of AKI in the CKD patient (see Fig. 14.2, Panel B). For instance, need for mechanical ventilation can have a deleterious effect on renal function via direct hemodynamic effects and inflammatory mechanisms.[18] Positive pressure ventilation is associated with increased in intrathoracic pressure, reduced venous return, increased pulmonary vascular resistance, right ventricular dysfunction causing reduced cardiac output, hypotension, and peripheral hypoperfusion at the same time as increasing central venous pressure and resultant renal venous congestion. Such hemodynamic effects will be occurring in critically ill patients who potentially already have abnormal renal perfusion, or coexisting risk factors such as intraabdominal hypertension[9] or abnormal neurohormonal responses.[19,20] Beyond its direct hemodynamic effects multiple proinflammatory effects of invasive mechanical ventilation have been associated with an increased susceptibility for the development of AKI in critical illness.[21]

The intimate relationship between CKD and cardiac disease similarly may predispose patients with heart disease to AKI during acute illness. Up to 63% of cases of heart failure have some degree of CKD.[10] Accelerated coronary artery atherosclerosis is observed in CKD, predisposed by chronic hypertension, dyslipidemia, altered calcium/phosphorus metabolism, and increased vascular stiffness.[13] Uremic cardiomyopathy is characterized by structural and electrophysiologic heart remodeling, leading to biventricular hypertrophy, systolic and diastolic dysfunction, myocardial capillary rarefication, chronic myocardial ischemia, and cardiac fibrosis.[22] These manifestations can occur relatively early in the course of CKD, well in advance of classical manifestation of profound uremia, such as pericarditis, which is rare in the modern era.

Beyond the accelerated chronic cardiovascular disease seen in CKD patients (see Fig. 14.2 Panel C), development of acute heart failure may be associated with acute deterioration leading to multiorgan impairment and a spiral deterioration in renal and cardiac function.[13,23,24] As well as the direct forward and backward effects of cardiac failure on distant organ function, other potential pathophysiologic mechanisms include pathophysiologic neurohormonal responses to cardiac dysfunction, systemic inflammation, impaired immunity, and toxic compounds including sources of circulating catalytic iron[23] (see Fig. 14.2, Panel D).

ACUTE KIDNEY INJURY AND THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Considerable epidemiologic evidence now exists to implicate AKI as a major risk factor for development of CKD[25–28] and especially for CKD progression in those with a background or preexisting CKD.[26] Episodes of AKI requiring renal replacement therapy (RRT) may confer the highest risk of CKD, with a 28-fold increase in risk of developing stage IV or V CKD and more than a twofold increased risk of death during follow-up.[28] Finally, recurrent AKI is strongly associated with development of advanced CKD with a doubling of risk for each AKI episode beyond the first reported in a diabetic population[29] so that in many patients with CKD, progression may occur more as recurrent step-downs associated with AKI than a continuous slow decline.

However, despite this strong epidemiologic association between AKI and progression of CKD, this may not be apparent immediately after critical illness. In a cohort of patients who had AKI and recovered to normal serum creatinine, half went on to develop CKD by 36 months with an additional significantly increased risk of death compared with non-AKI controls over this period.[30] Difficulty in recognizing severity of CKD after AKI may account for very low reported rates of referral for nephrology follow-up.[31]

Progression of CKD involves common pathophysiologic processes involving the development of proteinuria, systemic hypertension, and glomerulosclerosis and tubulointerstitial fibrosis leading to a progressive decline in GFR. Chronic inflammation is thought to play an important role in the development of tubulointerstitial fibrosis, and this can occur as a sequela of acute inflammation during AKI.[32] After AKI, depending on the local inflammatory microenvironment, monocytes and lymphocytes may direct repair, regeneration, and tissue remodeling, or promote fibroblastic metaplasia, proliferation, and fibrosis. In patients with preexisting CKD, interstitial fibrosis is likely to predispose to further inflammation and fibrosis rather than resolution and healing, causing ongoing peritubular capillary rarefaction, local hypoxia, and progressive nephron loss, even after the acute insult has abated.

Once irreversible loss of nephron units has occurred, renal blood flow autoregulation to neighboring nephron units is impaired, allowing systemic blood pressure to be directly transmitted to glomerular arterioles. In combination with hypertensive systemic neuroendocrine responses, this causes intraglomerular hypertension and hyperfiltration, temporarily preserving GFR at the expense progressive arteriosclerosis, glomerulosclerosis, and tubular atrophy. Thus, after AKI, new or worsened chronic renal disease may be subtle but still of prognostic significance.

Diagnosis of persistent renal dysfunction as an outcome of AKI can be confounded by several factors. The use of creatinine-based eGFR in comparison with cystatin C, a renal filtration marker less dependent on muscle mass has been examined in large meta-analysis of outpatient data[33]; eGFR based on cystatin C better predicted all-cause mortality and cardiovascular death compared with that based on serum creatinine. These results suggest that variations in muscle creatinine generation may confound CKD diagnosis in the general population and that these missed diagnoses are clinically significant. This concern applies especially to survivors of critical illness in whom large acute falls in creatinine generation rate are observed in clinical settings[34] and animal models,[35] decreasing the rate of rise and the absolute creatinine increment after a fall in GFR.[36] Importantly, the largest falls in creatinine generation are associated with greatest illness severity.[34] These changes in creatinine generation are likely to be associated with the profound and progressive loss of skeletal muscle protein[37–39] and muscle thickness,[39–41] which accompany prolonged critical illness. Thus estimates of renal function after critical illness could fail to detect significant loss of

GFR and will not be directly comparable to a baseline creatinine. Irrespective of creatinine-estimated GFR, proteinuria is associated with increased all-cause mortality, cardiovascular mortality, progressive CKD, end-stage renal disease, and risk of new AKI, with increasing risk with more severe levels of proteinuria.[42,43] Thus proteinuria is a key prognostic indicator for progression of CKD after AKI at all levels of GFR as a reflection of chronic tubular injury and/or glomerular hypertension and hyperfiltration. Development or worsening of proteinuria after AKI would constitute strong evidence for progression of CKD, even if creatinine based GFR appears similar to premorbid baseline.

In the treatment of AKI, avoidance of recurrent renal injury is crucial to achieving maximal renal recovery so that the treatment of AKI merges into the prevention of CKD. Use of intermittent hemodialysis for RRT in AKI has been associated with poorer renal recovery than continuous modalities of RRT[44,45] possibly related to intradialytic falls in cardiac output with rapid ultrafiltration, causing renal hypoperfusion and recurrent ischemic injury.[46] However, a recent large US single-center retrospective study found no difference in renal recovery rate between continuous renal replacement therapy (CRRT) and intermittent hemodialysis (IHD) as initial RRT modality,[47] although in this center one third of patients initially treated with CRRT went on to have some exposure to IHD during their ICU stay. Because of these concerns, CRRT is the recommended treatment modality for hemodynamically unstable patients with AKI.[48] Given the increased risk of deterioration in renal function during AKI and their lesser renal reserve at baseline, this recommendation may especially apply to patients with CKD, who are at the highest risk of ESRD.

Given the diagnostic difficulties outlined, it is appropriate to consider all survivors of critical illness complicated by AKI at risk of more rapid CKD progression, particularly those who already had premorbid CKD. Thus, irrespective of the mildness of baseline CKD, or apparent recovery to baseline, all AKI survivors should be considered for follow-up involving monitoring of serum creatinine, blood pressure, urinalysis, and assessment of cardiovascular risk factors. Treatment of hypertension and modification of cardiovascular risk factors are central to management of patients with or at risk of CKD.[49] In patients with proteinuria, ACE inhibitors or AT-2 receptor blocking agents should be considered, because these may reduce proteinuria and the rate of progression of CKD.[50] Although patients should be counseled, appropriate caution should be taken with these medications in the context of new acute illnesses where there is a high risk of recurrent AKI.

MANAGEMENT END-STAGE RENAL DISEASE PATIENTS IN THE INTENSIVE CARE UNIT

Advanced age, the higher prevalence of peripheral vascular disease, cerebrovascular disease, ischemic and nonischemic cardiovascular disease, and diabetes mellitus complicate the care of critically ill ESRD patients. A recent systematic review has demonstrated cardiopulmonary edema and sepsis as the most frequent causes for ICU admission in this population,[51] whereas elective or emergency surgical are also frequent causes for ICU admission. Common triggers for acute respiratory failure requiring respiratory support include pneumonia, excessive interdialytic weight gain, and primary cardiac events.[52,53] Careful patient evaluation is essential because similar presenting features may require distinct clinical management depending on the underlying condition.

Sudden death, myocardial infarction, cardiac arrest, and malignant arrhythmias are the major cause of death in CKD/ESRD patients, accounting for 43% of all-cause mortality.[54] After cardiovascular disease, sepsis is the second cause of death in patients with CKD/ESRD.[55] ESRD patients have higher rates of infection with resistant microorganisms increasing the risk of failure and the costs of care[56] and are at higher baseline risk of infection resulting from attenuated innate and acquired immunity.[56–58] The most common sources of infection are indwelling hemodialysis or peritoneal dialysis catheters followed by lower respiratory tract infections.[59] The diagnosis and management of sepsis in ESRD patients is a clinical challenge because of impaired physiologic response to sepsis and susceptibility to fluid overload, often requiring invasive hemodynamic monitoring and early recourse to vasopressors. Finally, ESRD patients frequently require surgical procedures for indications directly related to and unrelated to their ESRD treatment. Major surgery is associated with an increased need for ICU support and with a greater morbidity and mortality in the ESRD population.[60]

In the ICU, acute RRT prescription and management for ESRD patient depend on chronic modality of RRT, vascular access, hemodynamic status, physician and staff experience, and ICU resources. Currently, most patients receive intermittent HD or CRRT using a temporary vascular access catheter.[61] Attention should be paid to volume management, electrolyte control, and preservation of vascular access for long-term chronic dialysis. Often critically ill ESRD patients with poor cardiac reserve do not tolerate fluid removal during intermittent dialysis and require CRRT to prevent progressive fluid overload and to enable effect RRT. However, use of CRRT may require insertion of a temporary dialysis catheter for those normally dialysing on an AV fistula or graft, which may be difficult to achieve in some, risks nosocomial infection, and may cause loss of future sites for vascular access. If intermittent hemodialysis is continued, then daily treatment with a significantly modified prescription may be required. Overall the management of the critically ill ESRD is challenging and must be individualized with close cooperation between intensivist and nephrologist. Nevertheless, many patients can have good outcomes particularly with readily reversible conditions such as line sepsis or fluid overload, and there should not be a reluctance to admit such patients to the ICU for these indications.

CONCLUSION

A significant proportion of patients have clinically manifested CKD at ICU admission. This ranges from subclinical forms of renal insufficiency (reduction of renal functional reserve) to patients with ESRD already on chronic dialysis treatment. These patients suffer from increased risk of complications because of chronic kidney dysfunction and other associated comorbidities, in particular, the development of acute-on-chronic kidney disease. Importantly, patients suffering from one or more AKI episodes are at increased risk for development of CKD and eventual ESRD other time, and such progression often is associated with recurrent AKI. All these aspects require a multidisciplinary approach to the management and follow-up of the critically ill patient with kidney problems.

Key Points

1. Patients with chronic kidney disease (CKD) are now frequently admitted to the intensive care unit (ICU) and are at increased risk of multiorgan failure, death, and the during critical illness.
2. CKD is the strongest risk factor for the development of acute kidney injury during critical illness.
3. AKI is associated strongly with the development and progression of CKD; however, the presence and severity of CKD may not be fully manifest immediately after critical illness, demanding specific follow-up.
4. Patients with end-stage renal disease admitted to ICU are at high risk, have special requirements, and need multidisciplinary management.

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