Long-term sequelae of acute kidney injury in the ICU

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Purpose of review
Acute kidney injury (AKI) in the ICU is associated with adverse outcomes. We review the long-term consequences of AKI in ICU patients.

Recent findings
Observational studies show associations between AKI and mortality, prolonged length of ICU stay, dependence on mechanical ventilation, the development and progression of chronic kidney disease (CKD), and need for permanent renal replacement therapy. Few studies evaluate ICU AKI outcomes specifically, and data on long-term outcomes of survivors from this population are sparse. Little information exists comparing AKI in ICU and non-ICU settings, and prospective study designs to address such questions are problematic. AKI in the ICU should be distinguished from AKI in other clinical settings, as the underlying pathophysiology, severity of illness, and risk for permanent sequelae may be different. AKI and CKD are not mutually exclusive, but are part of a clinical spectrum in which AKI can potentiate the risk for CKD and pre-existing CKD increases risks of AKI.

Summary
Further research is necessary to delineate the mechanisms by which AKI may lead to CKD, and to understand how CKD enhances the risk for developing AKI. Whereas restrospective observational studies of this population exist, prospective clinical studies and trials evaluating the long-term clinical outcomes of AKI specifically in ICU patients are needed.

Keywords
acute kidney injury, chronic kidney disease, survival

INTRODUCTION

The incidence of acute kidney injury (AKI) has continued to increase, particularly in critical care settings [1▪,2,3]. With AKI definitions based on Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria, more patients are being diagnosed with this condition [4,5]. Strong associations have been made between the development of AKI and adverse clinical outcomes, including increased mortality, and the development of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1▪,2–5,6▪–9▪,10], highlighting the significant public health burden AKI presents. Previously felt to usually be a completely reversible condition, increasing observational data over the past decade suggest AKI increases the risk for permanent kidney damage, acute kidney disease, and subsequent development of CKD [1▪,2,3,6▪–9▪,10–12]. Patients at greater risk for the development of AKI, such as those with sepsis, may be more likely to be treated in an ICU setting. AKI in the ICU is presumably of greater severity than that encountered in other clinical settings, but comprehensively collected, unbiased, and valid clinical information on this issue is necessarily limited [13,14]. ICU patients with acute renal failure (ARF) were younger, more likely to have acute tubular necrosis (ATN), and were less likely to have prerenal azotemia or urinary tract obstruction, but were more likely to be treated with

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KEY POINTS

- Acute kidney injury (AKI) is a major risk factor for developing chronic kidney disease (CKD) and CKD significantly increases the risk of developing AKI.
- AKI and CKD are likely not two separate clinical entities but represent a continuum of the same disorder.
- AKI in the ICU should be distinguished from AKI in other clinical settings.
- AKI in the ICU significantly increases the risk for mortality and need for permanent renal replacement therapy.
- Few long-term data exist on outcomes of high-risk groups who sustain AKI in ICU settings, such as neonatal and pediatric patients, the elderly, and those with sepsis.

renal replacement therapy (RRT) than an ARF population in non-ICU settings [13]. Although some studies suggest ARF might affect a wide and variable range of ICU patients [3,15,16], one large study, using contemporary criteria for definitions, suggested about a third of ICU patients developed AKI in a national sample between 2000 and 2005 [1▪,17].

ACUTE KIDNEY INJURY AND INCREASED MORTALITY

Many epidemiologic studies have linked AKI and mortality. The AKI mortality rate in the ICU is greater than 50% in several studies [1▪,3,15,16]. Increased mortality risk may be related to higher rates of cardiovascular events, including congestive heart failure (CHF) as a result of total body volume overload, higher rates of myocardial infarction, a greater number of ventilator-dependent days, and the effects of uremia to impair the immune system, thereby limiting appropriate physiologic responses to infection and sepsis.

A study of 523 390 patients in northern Scotland found an AKI incidence rate of 2147 per million [18]. Increased RIFLE stage was associated with greater hospital mortality rates, need for RRT, and hospital length of stay (LOS). Uchino *et al.* [3] found increased inpatient mortality in patients with higher RIFLE stages. The 'Risk' (R) RIFLE category carried an inpatient mortality odds ratio of 2.5 compared to those without AKI. Patients in the 'Injury' (I) category had a 5.4 odds ratio for hospital mortality. Those in the 'Failure' (F) category had a 10.1-fold increased risk for inpatient mortality compared to those without AKI [3].

Xue *et al.* [12] showed an association between a diagnosis of ARF and mortality in a retrospective cohort study of Medicare patients hospitalized between 1992 and 2001. The inpatient death rate was 15.2% if patients had ARF identified as a primary International Classification of Diseases (ICD)-9 diagnosis, 32.6% if ARF was a secondary diagnosis, and only 4.6% in patients without an ARF diagnosis. The mortality rate within 90 days of hospitalization was 34.5% in patients with ARF as a primary discharge diagnosis, 48.6% in those with a secondary ARF diagnosis, and 13.1% in patients discharged without a diagnosis of AKI.

In Australia, 120 123 ICU patients from January 2000 to December 2005 were studied [17]. The AKI incidence rate was 36.1%. After adjustment for multiple comorbid conditions, each RIFLE stage was independently associated with a progressively higher mortality odds ratio (R 1.58, I 2.54, and F 3.22). Whereas there are inherent limitations in drawing conclusions from observational studies, the reproducibility of results across multiple studies adds strength to the consistent finding that RIFLE criteria are strong independent mortality risk factors.

SEPSIS AND ACUTE KIDNEY INJURY

A majority of AKI in the ICU can be attributed to sepsis. Several studies estimate 45–70% of ICU AKI is related to sepsis [3,11,17,19,20,21▪,22]. The increased incidence of AKI may be due to the increased incidence of sepsis [11]. Sepsis-associated AKI (SA-AKI) is different from AKI related to other causes [21▪,22]. Patients with SA-AKI had inferior outcomes with respect to severity of illness, mortality, prolonged need for mechanical ventilation, use of vasopressors, and hospital LOS, compared to AKI patients without sepsis [17]. Sepsis accounted for 833 of 1753 (47.5%) ICU patients from multiple centers who developed AKI. There was no significant difference in the proportion of patients requiring RRT between AKI patients with and without sepsis. Patients with SA-AKI had a median survival of 14 versus 31 days for patients with nonseptic AKI. After multivariable adjustment, ICU LOS was approximately 1 week longer in those with SA-AKI. SA-AKI independently predicted hospital mortality and had a significantly higher crude case fatality rate of 70.2 versus 51.8% for nonseptic AKI patients.

The underlying pathophysiology of SA-AKI is believed to encompass multiple hits that involve inflammatory, apoptotic, and ischemia-reperfusion renal injury pathways [21▪,22–26]. Elevated levels of pro-inflammatory and anti-inflammatory

cytokines, an altered coagulation cascade, and endothelial dysfunction all may play synergistic roles in the 'initiation, maintenance, extension, and recovery phases' of SA-AKI [23–26]. Specific treatments designed to enhance or inhibit these pathways may play therapeutic roles in potential approaches for treatment of SA-AKI [21▪].

Patients with AKI in the ICU represent a unique, selected, and biased study group with often inferior and distinct clinical outcomes compared to hospitalized non-ICU patients without sepsis. Relatively few data regarding progressive renal dysfunction, cardiovascular disease, and other long-term complications in this specific population have been generated by carefully designed, prospective longitudinal studies. Therefore, when analyzing studies that evaluate AKI outcomes, it is important to distinguish ICU from non-ICU patients. More studies are needed to focus on this particular group of ICU patients with AKI.

ACUTE KIDNEY INJURY AND THE RISK OF PROGRESSION TO CHRONIC KIDNEY DISEASE

Studies support the concept that AKI is a major risk factor for the development of CKD [6▪–9▪,10–12]. Amdur *et al.* [10] evaluated the outcomes of 79 000 inpatients in the Veterans Affairs Medical Center clinical database. Five thousand four hundred and four patients were diagnosed with ARF or ATN based on ICD-9 codes. Patients were excluded from the study if they had pre-existing CKD. Patients with ARF or ATN were significantly more likely to progress to CKD over a 5-year follow-up period, compared to a control group composed of inpatients with myocardial infarction or pneumonia, but without AKI. Compared to the control group, AKI patients were at higher risk for progressing to CKD stage 4 and had a higher mortality rate.

These investigators evaluated 5351 veterans with AKI defined by ICD-9 codes from 1 October, 1999 through 31 December, 2005, and developed a model evaluating variables likely to predict progression of AKI to CKD [7▪]. They found severity of AKI defined by RIFLE criteria, hypoalbuminemia, diabetes, and increased age were all independently associated with progression to CKD.

In 233 803 Medicare patients hospitalized in 2000 [11], 3.1% were diagnosed with AKI. AKI patients had an eight-fold higher risk for progressing to ESRD. After multivariable analysis, the hazard ratio for ESRD was 41.2 in patients with AKI and CKD, 13.0 with AKI without baseline CKD, and 8.4 for patients who had CKD but no AKI.

In a Kaiser Permanente database, 556 090 Northern California patients hospitalized over an 8-year period who had a baseline estimated glomerular filtration rate (eGFR) greater than 45 ml/min/1.73 m^2 were studied [27]. Seven hundred and three developed dialysis-dependent AKI. Over 10 344 person-years of follow-up, dialysis-dependent AKI was associated with 28-fold increased risk for progressive CKD, and double the mortality risk compared to patients without AKI. Whereas limited by its observational nature, this study emphasizes the long-term clinical consequences of being diagnosed with AKI.

In a population-based cohort study in Ontario [28], 3769 patients who developed AKI and required acute inpatient dialysis, but subsequently recovered renal function allowing discontinuation of dialysis between 1 July, 1996 and 31 December, 2006 were identified, with 13 598 matched controls. Hospitalized patients with dialysis-dependent AKI had an adjusted hazard ratio of 3.23 for ultimately needing chronic dialysis therapy. There was not an increased risk for all-cause mortality in patients who developed AKI. Differences in study design, healthcare systems and delivery, and the patient populations likely account for the disparate mortality outcomes.

These studies show AKI should be considered among the classic risk factors for CKD, as well as diabetes and hypertension. Clinicians evaluating patients for CKD should review the patient's history for previous AKI episodes.

SEVERITY OF ACUTE KIDNEY INJURY AND RISK FOR CHRONIC KIDNEY DISEASE PROGRESSION

Several studies identified links between the severity of AKI and the risk for CKD progression [7▪–9▪]. Fourteen thousand seven hundred and eighty-two patients underwent coronary angiograms between 2004 and 2006 [29]. AKI was assessed based on AKIN staging criteria. One thousand and ninety-nine patients had stage 1 AKI and 321 patients developed stage 2 or 3 AKI. The adjusted hazard ratio for death increased with advancing AKIN criteria stages (2.00 for AKIN stage 1, 3.72 for AKIN stage 2 or 3). There was also an increasing risk of developing ESRD across the AKIN stages. In patients with AKIN stages 2 or 3, there was a greater than 11-fold increase in the risk for developing ESRD. There was also a progressive increase in the rate of subsequent hospitalizations for cardiovascular and renal events across the AKIN stages.

In 29 388 cardiac surgery patients at Veterans Affairs Hospitals over a 6-year period, increase in serum creatinine concentration (SCr) from baseline was evaluated [30], and was stratified into four categories. Outcomes were assessed 3 months after surgery. There was a graded increase in the hazard

ratios for incident CKD, progression in CKD stage, and long-term mortality across the SCr categories.

Chawla *et al.* [7▪] showed a correlation between the severity of AKI and CKD progression. In 11 589 patients, the severity of AKI, measured by peak SCr, was associated with progression to more advanced stages of CKD. If patients required acute dialysis, there was a significantly higher risk for progressive CKD compared to patients with less severe AKI.

ACUTE KIDNEY INJURY CAN ACCELERATE PRE-EXISTING CHRONIC KIDNEY DISEASE

An episode of AKI can lead to faster progression of pre-existing renal insufficiency. CKD patients who developed AKI had a 41 times higher likelihood of progressing to ESRD compared to patients with no baseline decrement in GFR [11]. Patients with CKD and no AKI had an 8.4-fold higher risk of developing ESRD. Therefore, a diagnosis of AKI superimposed on CKD increases the risk of ESRD by approximately four-fold. This issue has been the subject of a recent editorial [31].

The elderly, at risk for diminution of GFR, and with abnormal hemodynamics and a substantial burden of comorbidity, are at particular risk for developing AKI, and for subsequent complications [11,32]. Similarly, AKI episodes in pediatric patients enhance the progression of CKD. Thirty-four percent of pediatric ICU patients had decreased renal function or were dialysis-dependent upon discharge from a tertiary care center [33]. Patients were followed for 3–5 years after AKI diagnosis [33]. Mortality was almost 80%, with most deaths occurring in the first 2 years after diagnosis of AKI. Approximately 2/3 of patients that had outpatient follow-up showed some degree of CKD, evidenced by albuminuria, reduced eGFR, or hypertension. These results in pediatric patients are of particular importance in highlighting the independent role AKI may have in promoting the development of CKD, as they do not typically have other traditional adult risk factors for CKD, such as diabetes, hypertension, and vascular disease. Standard medical surveillance through adolescence may not concentrate on evaluation of renal function. It is interesting to speculate that the burden of CKD may relate in part to pediatric or neonatal episodes of AKI.

ACUTE KIDNEY INJURY IN THE PEDIATRIC/NEONATAL ICU

AKI is common in pediatric ICUs and is associated with increased morbidity and mortality [34]. Forty-one AKI cases were identified in a cohort of 229 low-birth-weight infants followed until 36 weeks [35]. Seventeen of the 41 patients who developed AKI died compared to 5% of those without AKI. Of 430 infants with congenital heart disease who underwent cardiopulmonary bypass, 52% developed AKI [36]. AKI patients had increased ICU LOS, need for mechanical ventilation, and inotropic support. Twelve percent of AKI patients died compared to 3% of those without AKI. Among 7941 neonates in a cohort that received extracorporeal membrane oxygenation (ECMO), the mortality odds ratio was 3.2 in neonates who developed AKI compared to those without AKI [37]. Neonates who required RRT had a 1.9 times higher risk of death compared to neonates not requiring RRT. AKI was identified based on RIFLE criteria in 48 of 68 (71%) pediatric patients who required ECMO [38]. In AKI patients, there was increased mortality, dependence on ECMO, and ventilator-dependent days.

There are several important considerations when evaluating the epidemiology of AKI in the neonatal ICU. Oliguria is uncommon in neonates; therefore urine output is not a sensitive AKI indicator [34]. Alterations in SCr are unreliable since neonatal levels of SCr initially coincide with maternal values, which ultimately undergo a variable decrease weeks after birth [34], limiting the sensitivity of SCr in identifying neonatal AKI episodes. This unique patient population requires further study, particularly to elucidate specific independent mechanisms through which AKI can lead to CKD.

MECHANISMS OF ACUTE KIDNEY INJURY LEADING TO CHRONIC KIDNEY DISEASE

Observational studies support a role for AKI in promoting permanent renal damage; however, the precise underlying pathophysiologic mechanisms are unclear. Speculation has centered on the development of nephron loss following an AKI episode, which may lead to glomerular hyperfiltration, tubulointerstitial fibrosis, arteriosclerosis, and glomerulosclerosis [8▪,39–42]. Nephron loss following AKI may be similar to that following a nephrectomy, leading to glomerular hypertrophy in animal models [8▪,39–41]. AKI also promotes endothelial cell injury. The resulting vascular dropout can lead to permanent renal damage [43].

There is an important role for inflammation in AKI, especially in ischemic ATN [44–47]. Animal models of early-phase ATN are characterized by an interstitial neutrophil infiltrate, whereas in later phases, monocytes appear, which may mediate development of tubulointerstitial fibrosis.

Regeneration of renal tubules occurs in ATN recovery phases; however, depending on the nature of the initial injury and the degree of monocytic infiltration, patchy areas of interstitial fibrosis may develop, leading to permanent renal damage [8▪,39,48].

Disruption of cell cycle repair mechanisms during recovery phases of AKI may impair tubular regeneration, leading to fibrosis [8▪,39,48]. Animal models support a role for cell cycle abnormalities leading to CKD. Specific cell cycle inhibitors may worsen AKI outcomes in animal models [8▪,39, 49,50]. If the normal cell cycle is disrupted, renal tubular cells may transform into fibroblasts which promote tubulointerstitial fibrosis [39,51,52].

PREDICTORS OF ACUTE KIDNEY INJURY PROGRESSION TO CHRONIC KIDNEY DISEASE

Chawla *et al.* [7▪] developed a clinical model for risk factors likely to be associated with progression from AKI to CKD. In multivariable analysis, variables including the need for dialysis, baseline eGFR, serum albumin concentration, and RIFLE stage all were associated with development of CKD following an AKI episode. Patients who required dialysis had a 500-fold increase in the risk of subsequent development of CKD. These factors are important to consider when determining which patients require close outpatient renal follow-up.

IMPACT ON CLINICAL PRACTICE

Given the significant potential for adverse downstream consequences resulting from an episode of AKI in the ICU, intensivists should pay close attention to increases in SCr that may result from therapeutic interventions, such as overly aggressive diuresis that may be used to treat patients presenting in volume overloaded states. Whereas there may be clear advantages to maintaining patients in a euvolemic state or in net negative fluid balance, particularly in the setting of CHF, adult respiratory distress syndrome (ARDS), and other causes of acute respiratory failure, consideration should be given to the growing evidence that the development of AKI has a deleterious effect on the morbidity and mortality of ICU patients. In addition, volume overload and other causes of prerenal azotemia, in addition to changes in renal function associated with nephrotoxic drugs, might have long-term adverse consequences. Close monitoring of volume status through invasive hemodynamic monitoring and accurate recording of hourly urine output are essential in an effort to prevent ischemic AKI in the ICU. Prospective studies on these issues must be performed to inform proper future practice.

CONCLUSION

AKI represents a major public health burden and is increasing in incidence. The clinical presentation of AKI in the ICU is different from that in other clinical settings, usually representing more severe disease. AKI is associated with high mortality rates, especially in ICUs, where SA-AKI predominates. AKI poses a significantly increased risk for development and progression of CKD, especially in patients with higher AKIN or RIFLE stages, and in those who require acute RRT. More studies are needed regarding the natural history and long-term follow-up, specifically of ICU patients who develop AKI. In addition, outcomes of elderly and pediatric patients, as well as neonates who develop AKI in ICU settings, should be determined.

The National Institute of Diabetes, Digestive and Kidney Diseases supports a long-term observational study of patients with AKI, and appropriate hospitalized control participants without AKI. The Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury Study (ASSESS AKI) will determine outcomes separately for ICU and non-ICU patients, including renal functional outcomes and the development of cardiovascular complications in adult and pediatric patients [53].

AKI and CKD are likely not two separate, mutually exclusive entities, but can be thought of occupying a continuum of the same disorder. Further research is required to ascertain the precise mechanisms by which AKI may lead to CKD. Outpatient renal follow-up is necessary in patients following an AKI episode in the ICU, as they are at increased risk for future development of CKD. Clinical attention should be directed to and future studies should focus on preventive measures to slow the progression of renal impairment, for instance, optimizing the use of renin-angiotensin inhibitors, statins, blood pressure and glycemic control, and low-sodium, low-protein diets. Prospective clinical trials are necessary to precisely identify which AKI patients are most likely to develop CKD.

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Conflicts of interest

The views expressed here do not necessarily represent the views of the Department of Health and Human Services, the National Institutes of Health, the National Institute of Diabetes and Digestive and Kidney Diseases, or the United States Government.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 722).

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