CHAPTER 23

Acute Kidney Disease, Renal Recovery, and Post–Acute Kidney Injury Care

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OBJECTIVES

This chapter will:

1. Recognize acute kidney injury is associated with significant long-term clinical outcomes.
2. Review the evidence for acute kidney injury as a cause of chronic kidney disease.
3. Critically assess the concepts of acute kidney disease and renal recovery.
4. Develop a rationale for post–acute kidney injury care.

Over the first two decades of the millennium, uniform definitions for acute kidney injury (AKI) in the form of Acute Kidney Injury Network (AKIN); risk, injury, failure, loss, and end-stage renal disease (RIFLE); and Kidney Disease: Improving Global Outcomes (KDIGO) criteria have improved our understanding of the prevalence of AKI and associated clinical outcomes.[1,2] It is generally accepted that AKI complicates a large portion (15%–20%) of hospitalizations, with rates of 30% to 40% in the critically ill.[3] The enormous number of individuals afflicted with AKI represents a significant public health burden, because the potential for associated morbidity and mortality after AKI has been recognized increasingly. Death, major cardiovascular events, and chronic kidney disease (CKD) have been associated with a previous episode of AKI. With the difficulties inherent to conducting trials before the initiation phase of AKI, minimal gains made in changing the natural course of AKI during the maintenance phase[4] and lack of an approved drug for treatment of AKI[5], interventions aimed at the recovery phase of AKI may yield clinical benefits. AKI outcomes, associated sequelae, recognition, and management of individuals after AKI are reviewed as well as future directions for post–AKI care.

ACUTE KIDNEY INJURY AND ASSOCIATED OUTCOMES

Mortality

Multiple large observational studies have shown associations between AKI and mortality in hospitalized patients. AKI is a well-established independent risk factor for death in hospitalized patients.[6,7] Furthermore, mortality has been associated with increasing severity of AKI[8] with 28-day mortality rates of approximately 50% in individuals with severe AKI.[9] A number of risk factors for AKI have been identified, which could be subdivided into *nonmodifiable* (i.e., patient level factors such as age, diabetes, hypertension, chronic kidney disease, cardiovascular disease, liver disease, lung disease) and *modifiable* (i.e., exposures such as sepsis, radiocontrast exposure, trauma, cardiac surgery).[10] Traditional risk factors for AKI are similar to CKD, but sepsis-associated AKI is connected with particularly high mortality rates.[11]

More recently, findings of increased morbidity and mortality that occur months to years after an episode of AKI have been found consistently in large epidemiologic studies in a variety of patient populations.[12–14] It may not be surprising for clinicians that increased severity of AKI and requirement of renal replacement therapy (RRT) are associated with an increased risk for CKD and death,[15,16] but even milder forms of AKI have increased associated morbidity and mortality. These studies have upended the traditional view that AKI survivors returned to baseline or near baseline renal function without additional long-term consequences. Residual confounding certainly may account for these findings, and AKI may simply be a marker for increased risk. Future studies will help better define the relationship between AKI and outcomes. A recent propensity score-matched cohort method study showed increased risk for mortality and development of CKD and end-stage renal disease (ESRD) in patients with a reversible AKI defined as an estimated glomerular filtration rate (eGFR) back to within 90% of baseline and no previous evidence of renal disease.[17]

Cardiovascular Disease

CKD has been associated with worse cardiovascular (CV) outcomes in a number of settings.[18–20] In addition, AKI in the setting of myocardial infarction (MI) increased long-term morbidity and mortality.[12,21] Goldberg et al. showed that even small changes in renal function during acute myocardial infarction are related closely to long-term mortality and heart failure.[22] However, AKI as an

independent CV risk factor has not been appreciated until recently.

Chawla et al. examined the more than 35,000 US veterans with admission diagnoses of AKI or MI between October 1999 through December 2005 and observed outcomes for up to 6 years.[23] The combination of major adverse kidney events (MAKE), major cardiovascular events (MACE), and their combination, major adverse renocardiovascular events (MARCE), was assessed. The most deaths occurred in the MI+AKI group (57.5%), and the fewest (32.3%) occurred in patients with an uncomplicated MI admission. In the unadjusted and adjusted time-to-event analyses, patients with AKI and AKI+MI had worse MARCE outcomes than those who had MI alone (adjusted hazard ratios, 1.37 [95% confidence interval, 1.32 to 1.42] and 1.92 [1.86 to 1.99], respectively). This large study in US veterans demonstrated that an episode of AKI alone was associated with worse outcomes than from an episode of MI alone.

In a matched study of 4869 patients in Taiwan who recovered from dialysis-requiring AKI, the incidence rates of coronary events were 19.8 and 10.3 per 1000 person-years in the AKI recovery and non–AKI groups, respectively.[24] AKI recovery was associated with higher risk of coronary events (hazard ratio [HR], 1.67; 95% confidence interval [95% CI], 1.36 to 2.04) and all-cause mortality (HR, 1.67; 95% CI, 1.57 to 1.79) independent of the effects of subsequent progression to CKD and ESRD. These studies highlight a relatively new observation regarding AKI risk. Not only are MAKE associated with AKI but also are MACE. The combination of MAKE and MACE —MARCE— is likely to be recognized in increasing numbers in AKI survivors.

Chronic Kidney Disease and End-Stage Renal Disease

A number of observational studies of AKI survivors have demonstrated a strong association between an episode of AKI with the subsequent development of CKD and progression to ESRD.[25]

CKD subsequent to AKI has several established risk factors. AKI in the elderly is associated with high risk for development of CKD.[26] Other identified risk factors include diabetes mellitus, decreased baseline glomerular filtration rate, severity of AKI, and a low concentration of serum albumin. Severity of AKI as well as "recovery pattern" of AKI appear to influence outcomes.[15,27] Sepsis survivors may have the worst outlook for long-term injury.[11] Clinical prediction models have been developed and will be discussed later in this chapter.[28,29]

The relation of AKI episodes and subsequent CKD has been explored further in recent studies. The extent of renal recovery after AKI may play a role in CKD development, mortality,[16] as well as the risk of long-term MACE.[30] Not only may AKI lead to CKD, but also an episode of AKI appears to accelerate CKD progression.[31,32] Recurrent AKI imparted cumulative risk for progression to advanced CKD in people with diabetes.[33] As expected, recurrent AKI is associated with significant comorbidities outside of age and presence of diabetes mellitus. Siew et al. found that the highest risks were a diagnosis of congestive heart failure (primary diagnosis), decompensated advanced liver disease, cancer with or without chemotherapy, acute coronary syndrome, or volume depletion.[34] Observations of nonlinear progression of renal disease and relatively rapid trajectories to ESRD in certain individuals raise concern that recurrent AKI, in vulnerable populations and at vulnerable times, may unduly accelerate kidney failure.

DEVELOPMENT OF CKD AFTER AKI (AKI TRANSITION TO CKD)

The strong association of AKI with subsequent CKD, even in those with no clear evidence of baseline CKD, has led to the hypothesis that AKI may be part of the causal pathway to CKD. Although the observational studies preclude drawing any conclusion regarding causality, several factors have propelled the growing belief that AKI leads to CKD, including progression to ESRD.[35] Early studies that measured creatinine or inulin clearances in select patients demonstrated reduced renal function in individuals after experiencing AKI.[36,37] Furthermore, beyond the strong and consistent association across various populations as cited earlier, more recent studies show a graded relationship for severity and duration of AKI with incidence of CKD.[16,38,39] Concern that AKI survivors who appear to develop incident CKD already have many traditional CKD risk factors at baseline (e.g., advanced age, diabetes mellitus, hypertension, hypercholesterolemia) is addressed partly by studies in pediatric populations who do not have the same premorbid burdens, which associate an episode of AKI with the later development of CKD.[40–42]

AKI as a cause of de novo CKD has some biologic basis that supports the growing observational data.[43] Animal models support AKI as a cause of permanent renal injury and renal failure.[44] Renal parenchymal injury from an episode of AKI leads to several pathways to permanent damage: inflammation and resultant fibrosis, endothelial injury and vascular rarefaction, cell cycle arrest leading to persistently activated fibroblasts and maladaptive repair.[39,45] Mitochondrial disruption and necroptosis are more recently recognized mechanisms of injury.[46] In addition to the potential mechanisms of renal injury after AKI, it is fairly well established that nephron loss from any cause leads to compensatory changes (increased single-nephron GFR) and glomerular hypertrophy, which increases risk for glomerulosclerosis.[47] These maladaptive processes continue to act on the kidneys, leading to progressive loss of renal function.

Despite remaining questions regarding residual confounding, inaccurate baseline measures of renal function, misclassification of AKI based on serum creatinine,[48] or ascertainment bias in AKI survivors, the concept of AKI and CKD as an interconnected syndrome has gained traction in the nephrology community. It has already been well established that CKD is a risk factor for AKI,[49,50] possibly resulting from impaired autoregulation and reduced renal reserve, as well as enhanced recognition of AKI in individuals with reduced creatinine clearance at baseline. The interconnection of AKI and CKD as risk factors for each other and for cardiovascular disease may prove to be a new paradigm for the analysis and management of renal disease in the future.

RECOGNITION AND DETECTION OF PERSISTENT RENAL INJURY AND RENAL RECOVERY

Several important renal specific outcomes are possible after an episode of AKI, ranging from complete recovery to baseline renal function to development of ESRD: (1) AKI to full recovery of renal function to baseline, (2) AKI to incomplete recovery of renal function but near normal resulting in subclinical chronic kidney disease (CKD), (3)

AKI to incomplete recovery of renal function resulting in CKD by KDIGO criteria, (4) nonrecovery of function leading to ESRD.[46] The four possible outcomes could apply to AKI in patients with or without preexisting CKD. A definition for renal recovery is required first before uniform detection of persistent renal dysfunction and categorization can be performed.

Although no consensus definition for renal recovery existed, early studies of AKI defined recovery in terms of requirement for RRT at time of hospital discharge. Obviously, this would not include individuals with less severe AKI who did not require RRT but are still at risk for substantial morbidity and mortality. Outside of recovery of enough renal function to obviate the need for RRT, the measurement of renal recovery has not been defined uniformly. Some studies defined complete recovery as a return of serum creatinine to within 20% of baseline, whereas partial recovery was anything short of continued dialysis dependence.[51] By the RIFLE criteria, nonrecovery, or loss, is defined as persistent complete loss of kidney function for greater than 4 weeks, whereas end-stage kidney disease is defined as complete loss of kidney function at 3 months after AKI development. Therefore the definition of recovery depends on the time frame (e.g., less than 4 weeks, less than 90 days).[52] The KDIGO AKI work group proposed the concept of "acute kidney disease" (AKD), defined as a GFR < 60 mL/min/1.73 m^2 or evidence of structural kidney damage for less than 3 months. This provides a bridge between AKI and CKD definitions. A time period bridging the AKI and CKD definitions between the onset of the initiation phase of AKI and 3 months later would focus on screening for markers of kidney damage (e.g., proteinuria) and/or reduced GFR in AKI survivors.[2]

The Acute Dialysis Quality Initiative (ADQI) consensus definition included a definition of renal recovery: complete recovery is return to their baseline RIFLE classification or within 50% of baseline creatinine, whereas partial renal recovery exists if there is a persistent change in RIFLE classification (R, I, or F) or failure to recover within 50% of baseline, but not persistent need for RRT.[53,54] The ADQI definition includes a time period to assess it (i.e., at discharge from ICU or hospital and 90 days after AKI). The degree of recovery and timing of recovery are associated with important clinical outcomes,[16,55] so definitions should incorporate this and be tested regarding ability to assess future risk.

Defining AKI and renal recovery by serum creatinine measures is problematic for several reasons. First of all, baseline creatinine is often unknown in hospitalized individuals. Serum creatinine values at hospital admission are influenced by the patient's illness, hemodynamics, volume status, and exposure to nephrotoxic agents. ADQI suggested computation of a presumed baseline creatinine using the Modification of Diet in Renal Disease (MDRD) equation and assuming an eGFR of 60 mL/min,[56] although this risks misclassification of patients by assuming normal renal function for individuals without established baseline serum creatinine.[51] Second, serum creatinine as an indicator of renal function is that it is unreliable in patients with critical illness and sepsis.[57–60] Discharge serum creatinine (from ICU or hospital) often is assessed to determine initial recovery and new baseline but may be influenced by medications, nutritional status, and muscle wasting associated with critical illness.

Development of proteinuria or albuminuria may be useful to define continued renal dysfunction, but baseline and follow-up measures are often unavailable for analysis in observational studies. Furthermore, lack of albuminuria is not sufficient to guarantee lack of renal injury or dysfunction. AKI survivors may have reduced renal reserve but normal serum creatinine and albuminuria. Indeed, even apparent recovery from AKI by serum creatinine measures is associated with increased risk of CKD stage III.[61] Currently available markers of renal injury other than creatinine and proteinuria include timed urine collections for creatinine clearance measurement, GFR estimation using cystatin C, and direct GFR assessment by radionuclide clearance[52] but have not been systematically studied to inform clinicians regarding degree of renal recovery.

Because of these limitations, there is a need for biomarkers to assist in detection of ongoing injury, repair, and recovery of renal function.[62] Novel biomarkers of renal injury used for early detection of AKI also may provide useful information regarding ongoing injury or nonrecovery of renal function. Koyner et al. showed tissue inhibitor metalloproteinase-2 (TIMP-2)/insulin-like growth factor binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI.[63] A combination of biomarkers TIMP-2/IGFBP7 with urine output and serum creatinine was superior to predicting dialysis at 9 months in patients with AKI.[64]

In the Follow-Up Renal Assessment of Injury Long-Term After Acute Kidney Injury (FRAIL-AKI) study, Cooper et al. followed 372 children (119 AKI positive and 253 AKI negative) who underwent cardiopulmonary bypass surgery for a mean duration of 7 years. Urine concentrations of IL-18 and liver-type fatty acid-binding protein (L-FABP) remained elevated 7 years after an episode of AKI despite no conventional evidence of CKD. These biomarkers were elevated significantly versus non–AKI individuals and healthy controls.[65]

CARE AFTER ACUTE KIDNEY INJURY

Need for Care After Acute Kidney Injury

Early concepts of AKI described it as a self-limited disorder with complete or near-complete recovery. Information gleaned from large and long-term observational studies now forms a different picture: AKI and CKD as interconnected syndromes as well as AKI as a marker of significant CV outcomes and mortality. Even if AKI does not play a causal role in CKD or CKD progression, it remains a strong independent marker of risk. The public health impact of the long-term outcomes of AKI is significant, particularly with the aging population. One estimate for the developed nations (United States, Canada, Western Europe, and Australia) is 1.5 million AKI survivors per year with approximately 15% to 20% who progress to advanced-stage CKD within 24 months, resulting in approximately 300,000 cases of advanced CKD per year.[39] Beyond increased long-term risk for major cardiovascular and renal outcomes, AKI survivors have an increased risk of hospital readmissions,[66] which highlights a need for clinical follow-up shortly after discharge for specialized care that would include care coordination and medical reconciliation.

Discharge planning and systematic postdischarge follow-up (for all hospitalizations or for designated at-risk individuals) show promise in reduction of hospital readmissions and possibly mortality[67] as well as improved access for vulnerable populations.[68] However, the data are limited largely to the elderly and patients with congestive heart failure. Although it may be reasonable to observe patients known to be at high risk for morbidity and mortality, few

AKI survivors see nephrologists after discharge. Small studies show very low rates of follow-up for individuals with AKI severe enough to require RRT.[69,70] Data from the US Renal Data System indicate only 16.1% of Medicare recipients who experienced in-hospital AKI were seen by a nephrologist by 6 months after discharge. The proportion of patients seen for follow-up care is higher among those with preexisting CKD, but even among this group with recognized kidney disease, fewer than 25% are seen within 6 months.[71]

Siew et al. examined the likelihood of nephrology referral among 3929 hospitalized patients with AKI in the US Department of Veterans Affairs database.[72] The cumulative incidence of nephrology referral in the 12-month surveillance period before dying, initiating dialysis, or experiencing an improvement in kidney function was 8.5%. Perhaps more surprisingly, the severity of AKI did not affect referral rates. These low reported referral rates for AKI survivors is particularly dramatic when compared with postdischarge follow-up rates for another high-risk condition, myocardial infarction.[73] Although limited data are available, early nephrology follow-up after AKI is associated with enhanced survival,[74] highlighting the urgent need for of further study and trials of post–AKI care.

Qualifying for Care After Acute Kidney Injury in a Specialized Clinic

Associational studies support the notion that, of individuals who experience AKI, those who require RRT are at higher risk for poor outcomes. Extended follow up of the Randomized Evaluation of Normal vs. Augmented Levels of RRT (RENAL) trial indicate that nearly one third of patients who experienced AKI, required RRT, and survived 90 days later, subsequently died in the 3½-year follow-up period.[4] Furthermore, approximately 40% of AKI survivors in the RENAL study had some level of micro- or macroalbuminuria. Based on existing data, it is reasonable to schedule a postdischarge clinical assessment in all AKI survivors who required RRT for any time period. Further refinement of this inclusion policy may be possible through associational data. For example, in a retrospective study of 4383 hospitalized patients who required temporary RRT, Harel et al. found that previous nephrology consultation, a history of CKD, a higher Charlson comorbidity index score, and preexisting hypertension were significantly associated with an increased risk of progression to chronic dialysis over a mean follow-up of 2.4 years.[75]

Individuals with lesser degrees of AKI may be more problematic in terms of selection for follow-up care. The finding that risk for significant clinical outcomes is increased for all AKI has led to the suggestion that an AKI event be added to the medical record to assist in future studies and designate enhanced risk for caregivers.[54] However, the large number of AKI survivors would likely overwhelm the current clinical capacity of nephrology and primary care clinics. Moreover, not all AKI survivors necessarily need care in a specialized clinic. A simple and practical clinical score to identify patients at high risk for CKD progression and mortality post–AKI is needed for risk stratification and to allocate health resources in a reasonable manner.

Prediction with clinical measures is relatively poor when using severity scores, but models using AKI severity and other traditional clinical measures hold promise. In an analysis of US veterans, the following risk factors for progression to advanced CKD were found: advanced age, low serum albumin levels, presence of diabetes, and severity of AKI, as assessed by RIFLE score or mean serum creatinine levels during hospitalization.[15] Other studies have identified similar risk factors, including previous nephrology consultation, a history of CKD, preexisting hypertension or cardiovascular disease, older age, recurrent AKI, and higher serum creatinine 1 year post–AKI. Biomarkers used for AKI diagnosis are under investigation as markers for recovery and nonrecovery as well.[76] The use of biomarkers for recovery with or without clinical factors is likely to be used in the future to accurately determine level of risk for AKI survivors.

As mentioned earlier, it is important to recognize that AKI can lead to several possible outcomes from complete recovery to ESRD. Fig. 23.1 illustrates this as a flow diagram and incorporates the concept of a post–AKI evaluation. Currently, a simple approach for follow-up of AKI survivors could be based on KDIGO AKI stages (e.g., all patients who received RRT or who developed KDIGO AKI stage II or III). Although AKI stage I also may have increased risk of significant clinical outcomes, it may not be reasonable to include this large population for specialized clinics. Other inclusion and exclusion criteria have been developed and used in established post–AKI clinics, which are worth consideration to avoid overlap of care. Box 23.1 lists criteria for the AKI Follow-up Clinic for adults at St. Michael's Hospital and the University Health Network in Toronto, Ontario, Canada.[77]

Certain patient factors may indicate closer follow-up, even with less severe AKI. The need to slow CKD progression to delay or prevent ESRD over a longer lifespan may be enough to warrant follow-up of all pediatric AKI survivors.[78] Data on individuals with high cardiac disease burden who suffer AKI have shed more light on their risk. For example, heart failure patients, particularly those with AKI on CKD in decompensated heart failure[79] are at very high risk for MARCE. AKI post–coronary artery bypass grafting has been studied in numerous trials and represents a special population with enhanced risk who would likely benefit from specialized post–AKI care.

Management of Acute Kidney Injury Survivors

Without a solid foundation of clinical trial data to guide the best management of the post–AKI period and AKI survivors in general, appropriate management of AKI survivors may be the greatest question in AKI. Nonetheless, the goals of any post–AKI care would include: (1) to promote renal recovery, (2) to diagnose and manage CKD, and (3) to reduce associated CV outcomes. Timing of the assessment

BOX 23.1

Inclusion Criteria
Kidney Disease: Improving Global Outcomes (KDIGO) stage II AKI and above (including need for dialysis)

Exclusion Criteria
Kidney transplant recipients. Baseline eGFR under 30 mL/min/1.73 m^2. Diagnosis of glomerulonephritis, vasculitis with kidney involvement, hemolytic-uremic syndrome, polycystic kidney disease, multiple myeloma. Palliation as primary goal of care. Patients with previously established and ongoing nephrology follow-up, including patients discharged with a persistent requirement for renal replacement therapy.

From Silver SA, et al. Ambulatory care after acute kidney injury: an opportunity to improve patient outcomes. *Can J Kidney Health Dis.* 2015;2:36.

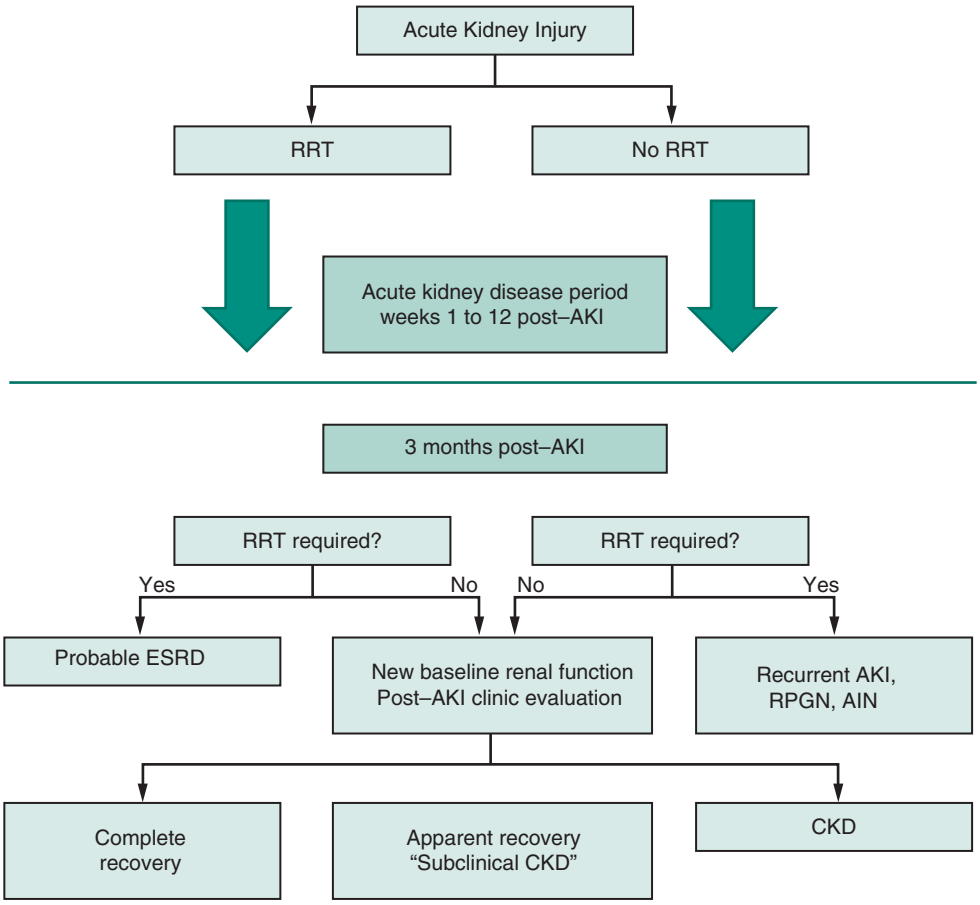

FIGURE 23.1 Renal outcomes after acute kidney injury. *AIN,* Acute interstitial nephritis; *CKD,* chronic kidney disease; *ESRD,* end-stage renal disease; *RPGN,* rapidly progressive glomerulonephritis; *RRT,* renal replacement therapy.

for renal recovery is an important aspect in post–AKI management, but there is no uniform consensus on a time point within the natural history of AKI as mentioned earlier. KDIGO defines AKD as a GFR less than 60 mL/min/1.73 m^2 for less than 3 months, or decrease in GFR by greater than 35%, or increase in serum creatinine by greater than 50% for less than 3 months. The commonly recommended time point of 90 days after an episode of AKI makes sense to determine recovery and risk, because that would be at the end of AKD period and thereby define if CKD is present.[16] Recommendations for stratifying recovery (within a certain percentage of baseline eGFR) at fixed interim points for establishing recovery (7, 30, and 90 days) and excluding early outcomes (up to 30, 90, and 180 days) has been recommended for future prospective studies.[80]

Although there are no proven interventions to assist in renal recovery, there are several reasons to direct AKI survivors to post–AKI care within the AKD period. Foremost, prompt outpatient follow-up after hospital discharge may enhance medication adherence, and it also provides an opportunity for timely medication reconciliation. Nephrology consultation early after discharge would include appropriate renal dosing of medications and avoidance of nephrotoxic agents. A key aspect, and source of concern, in the AKD period is the susceptibility to additional renal injury. Avoidance of recurrent AKI during the AKD period may prove to be of critical importance.

If CKD is diagnosed, standard-of-care treatments for CKD are reasonable in this high-risk population until clinical trial data eventually help guide practice for AKI survivors. Indeed, earlier referral to a nephrologist is associated with increased survival in those with CKD.[81] Furthermore, a diagnosis of CKD would justify standard interventions to reduce CV risk, such as hypertension control, inhibition of the renin-angiotensin-aldosterone axis, use of antiplatelet agents, and use of beta blockers if appropriate. Even without evidence for CKD, the fact that an episode of AKI has been associated with significant CV outcomes as outlined earlier makes CV risk assessment a reasonable approach in this vulnerable patient population. After an initial post–AKI clinical evaluation, either in a specialized clinic or with multidisciplinary clinic, follow-up criteria are needed. Some patients may be sent automatically to general nephrology based on CKD criteria or risk for ESRD. Some may be followed for a set period of time to determine stability and ensure maximal standard medical therapy before being discharged. Presumably, the lowest-risk individuals would be referred back to their primary care physician if they did not meet criteria for general nephrology care.

Obstacles to Care After Acute Kidney Injury

Establishment of criteria for eligibility for a post–AKI clinic is a challenge, but logistic issues in post–AKI care may be a greater one. Identification of incident AKI, notification of patients and healthcare providers of an AKI event, scheduling of an appointment with a post–AKI clinic, and ensuring patient adherence to post–AKI clinics are necessary aspects of any program. Undoubtedly, some in-hospital AKI survivors

are not seen by the nephrology service. Furthermore, the finding that community-acquired versus hospital-acquired AKI led to similar poor outcomes in several studies[82,83] suggests that all AKI survivors, inpatient and outpatient, may benefit from specialized post–AKI follow-up.

Significant changes to the normal process of care in health systems are likely needed to capture most, if not all, AKI survivors. The largely asymptomatic nature of AKI and the post–AKI period, combined with the frequent association of major comorbidities, particularly in the critically ill population, will likely be a barrier to post–AKI care. Other diseases may compete for patient attention and time. Poor functional status or cognitive impairment may play a role in nonadherence to recommendations for post–AKI care. Initial data demonstrate that an automated referral process increased the percentage of follow-up at 90 days for post–AKI clinic in Toronto.[84] The costs incurred by any post–AKI program may be a potential barrier to its implementation; therefore cost-effective analyses of post–AKI interventions should be part of ongoing and future trials.

Many questions are still unanswered because of lack of a good clinical evidence base. What other evaluations should be performed on initial presentation to the post-AKI clinic and on follow-up? How long should AKI survivors be monitored before discharge from the post–AKI clinic? Which referrals are appropriate for AKI survivors (e.g., other nephrology clinics such as pre-ESRD clinic or glomerulonephritis clinic, cardiology. coordination with primary care providers)?

SUMMARY AND FUTURE DIRECTIONS

There is still much to be learned about AKI survivors that cannot be gleaned from large administrative data sets. The connection between AKI with future morbidity and mortality will be elucidated further with more uniform and complete data obtained from a number of large, multi-center observational trials currently underway and should provide much needed data to help more accurately determine the role of AKI in mortality as well as a host of comorbidities, known and unknown. The ongoing Assessment, Serial Evaluation, and Subsequent Sequelae in AKI (ASSESS-AKI) consortium evaluates the long-term outcome of hospitalized patients, with and without CKD, who experience an episode of AKI. The natural history will be observed to determine the two primary aims:

1. Determine if AKI survivors have a greater risk of developing chronic kidney disease or worsening of pre-existing chronic kidney disease than hospitalized persons without AKI
2. Determine if AKI survivors have a higher risk of death, cardiovascular events, and other adverse events after hospital discharge than matched persons who did not suffer AKI during hospitalization

The Protocolized Goal-Directed Resuscitation of Septic Shock to Prevent Acute Kidney Injury (ProGRess AKI) study will follow subjects from the Protocolized Care for Early Septic Shock (ProCESS) study after hospital discharge to better understand the long-term effects of sepsis, particularly on the kidney and heart. ProGReSS AKI will focus on two important complications: recovery of kidney function and cardiovascular consequences of sepsis. Patients with and without AKI will be followed. Pediatric AKI survivors will be tracked in the Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology (AWARE) study,[85] a prospective observational study of more than 5000 critically ill children admitted to 31 pediatric intensive care units (PICUs) worldwide.

Some of these studies will obtain blood samples to assess the performance of AKI biomarkers in the prediction of clinically important outcomes. The At Risk in Derby (ARID) study, a UK single-center, observational, case-control study that aims to recruit 1084 hospitalized patients to determine the long-term outcomes for AKI survivors, will take blood and urine samples at 3, 9, and 33 months after an episode of AKI. The Translational Research Investigating Biomarker End-Points for AKI Study (TRIBE-AKI), is a multicenter prospective observational study sponsored by the National Heart Lung and Blood Institute to investigate novel biomarkers in the detection of early AKI after major cardiac surgery with a goal recruitment of 1500 individuals. Finally, information from single-center post–AKI discharge clinics such as the Nephrologist Follow-up Versus Usual Care After an Acute Kidney Injury Hospitalization (FUSION) study will help to determine if structured post–AKI follow-up can reduce major adverse kidney and cardiac events and assist in the design of pragmatic trials in the future.

Key Points

1. Acute kidney injury (AKI) is strongly associated with mortality and cardiovascular and renal outcomes, both in the short and long term.
2. Renal recovery after AKI presents an opportunity to improve subsequent overall health of AKI survivors and should be monitored by healthcare providers.
3. More accurate methods to assess renal recovery are needed, which, in turn, will assist in improving the definition of renal recovery.
4. Systematic clinical follow-up in AKI survivors may improve health outcomes and is being piloted in a number of clinical sites and research protocols.

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

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