Acute Kidney Injury in Chronic Kidney Disease

8

Sharidan K. Parr and Edward D. Siew

Before You Start: Facts You Need to Know

- AKI is among the fastest growing kidney diseases.
- CKD and proteinuria are common and overlooked risk factors for developing AKI.
- Patients with a rapid course to ESRD often have nonlinear decline in kidney function involving one or more episodes of AKI.
- Ideally, long-term goals of care (including whether to initiate dialysis) should be discussed *before hospitalization*, particularly among frail and elderly patients with CKD.
- Diagnostic tests such as fractional excretion of sodium (FeNa) may be unreliable in patients with CKD.
- After an episode of moderate to severe AKI or those where recovery to baseline has not occurred, patients should be evaluated within 3 months for resolution or for new onset or worsening of CKD.

S.K. Parr, MD • E.D. Siew, MD, MSCI (✉)
Division of Nephrology and Hypertension,
Department of Medicine,
Vanderbilt University Medical Center,
Nashville, TN, USA
e-mail: sharidan.k.parr@vanderbilt.edu;
edward.siew@vanderbilt.edu

8.1 Introduction: The Growing Impact of AKI

8.1.1 Occurrence and Definition

The Centers for Disease Control and Prevention estimate that kidney disease is the eighth leading cause of death in the United States (US), which consumes 23 % of total Medicare expenditures. By 2030, two million people in the United States will develop advanced kidney failure, the prevention of which is a global public health concern. AKI, particularly when severe, has been recognized as an increasingly important risk factor CKD progression [1]. AKI is characterized by an abrupt decline in glomerular filtration rate (GFR). The recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury suggest that a minimal threshold for defining AKI should include an increase in serum creatinine of at least 0.3 mg/dl (26.5 μmol/l) within 48 h, a 1.5 times increase in the baseline value within 7 days, or urine volume less than 0.5 ml/kg/h for at least 6 h (Table 8.1) [2]. This change in paradigm has been largely driven by observations showing that even without overt kidney failure, smaller changes in serum creatinine independently associate with poor clinical outcomes (Fig. 8.1) [3]. These observations have also led to the recent changing of the term "acute renal failure" to "acute kidney injury." The severity of AKI is further staged by incrementally larger increases in serum creatinine values or the persistence or worsening of

M. Arici (ed.), *Management of Chronic Kidney Disease*,
DOI 10.1007/978-3-642-54637-2_8, © Springer-Verlag Berlin Heidelberg 2014

oliguria. As these definitions require close monitoring of serum creatinine or urine output, most literature comes from hospitalized populations. Incidence rates for AKI vary with the setting studied, ranging up to 9.6 % of general admissions and up to 45 % in the critically ill [4]. Population-based studies within industrialized countries estimate incidence rates of between 2,147 and 5,000 cases/million population/year [5].

Table 8.1 Staging of AKI

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline or increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) or initiation of renal replacement therapy or in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h or Anuria for ≥12 h

Source: Reprinted with permission from Macmillan Publishers Ltd and Nature Publishing Group: Kidney Disease Improving Global Outcomes [2]

While AKI can be associated with exacerbations of intrinsic kidney disease or systemic diseases that target the kidney (e.g., lupus), the majority of AKI in developed countries occurs as a consequence of an acute illness or procedures that either compromise perfusion (e.g., volume-deplet on, acute blood loss, major vascular surgery) or stimulate profound inflammation (e.g., sepsis) (Box 8.3). Medications directly toxic to the kidney (e.g., nonsteroidal anti-inflammatory drugs (NSAIDS), aminoglycosides, iodinated contrast) also contribute to up to 1/5 of cases [6]. In developing countries, where disease surveillance is not widely implemented, available data indicate a higher prevalence of diarrheal and infectious-related causes of AKI, particularly among children.

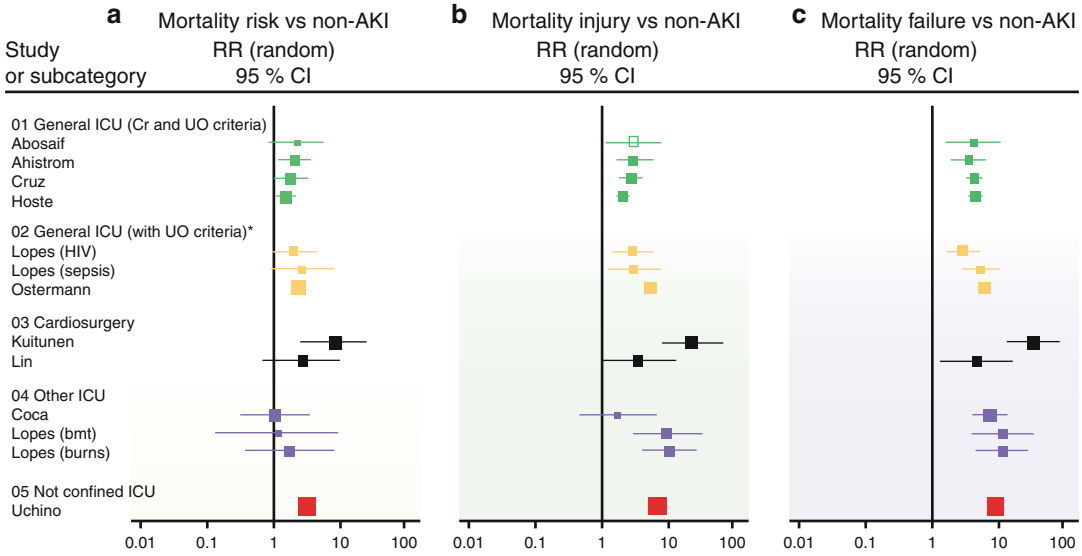


Fig. 8.1 Increased mortality risk associated with AKI extends to milder injury. Systematic review showing consistent increases in mortality risk associated with incrementally larger acute changes in serum creatinine in different acute care settings illustrated by Forrest plot. (**a**) Risk category denoted by a 50 % increase in baseline serum creatinine/25 % decrease in baseline GFR/urine output <0.5 mg/kg/h × 6 h (relative risk = 2.4), (**b**) injury denoted by a doubling in baseline serum creatinine/50 % decrease in GFR/urine output <0.5 ml/kg/h × 12 h (relative risk = 4.15), and (**c**) failure denoted by a tripling of baseline serum creatinine/GFR decrease of >75 %/acute increase in serum creatinine to ≥4 mg/dl with and acute rise of 0.5 mg/dl/urine output <0.3 ml/kg/h × 24 h/anuriax 12 h (relative risk = 6.37) (Reprinted with permission from Macmillan Publishers Ltd: Ricci et al. [3])

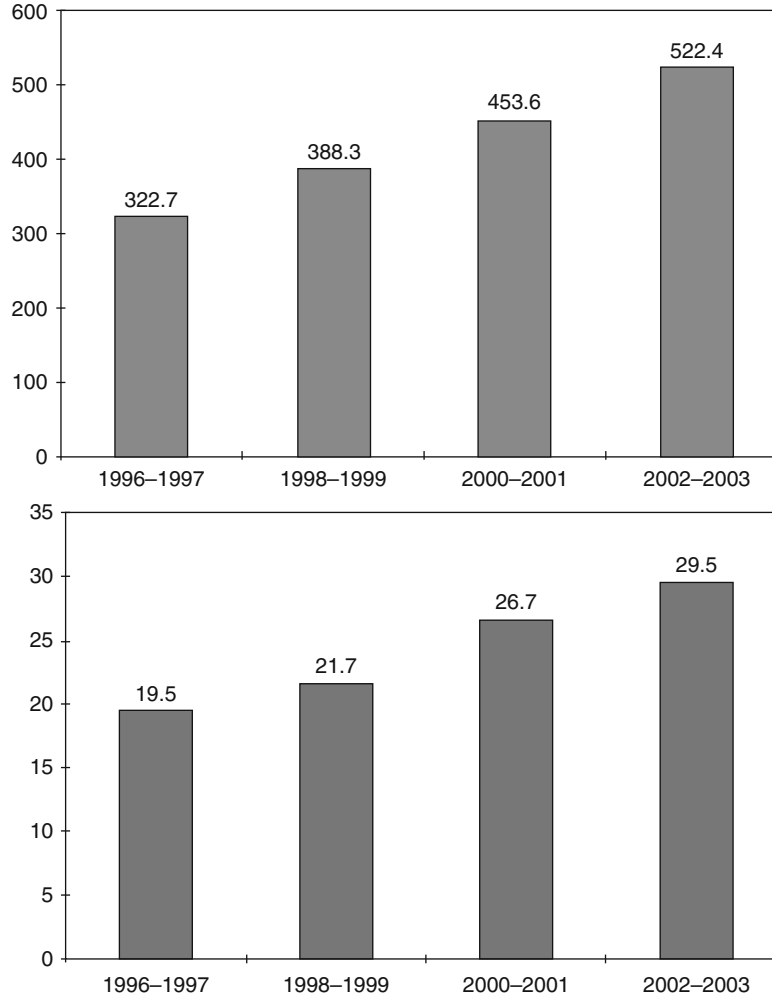


Fig. 8.2 The population incidence of dialysis and non-dialysis-requiring AKI in the United States is increasing. (**a**) Community-based incidence rates (per 100,000 person-years) of non-dialysis-requiring AKI per year. (**b**) Community-based incidence rates (per 100,000 person-years) of dialysis-requiring AKI per year (Reprinted with permission from Macmillan Publishers Ltd: Hsu et al. [5])

8.1.2 Prognosis

AKI is strongly associated with devastating short-term complications with mortality rates ranging from 28.1 % among those with easily recognizable forms of injury up to 60.3 % among critically ill patients who require dialysis [6]. Of greater concern are signals arising from both administrative and laboratory databases that the incidence of AKI is increasing rapidly (Fig. 8.2) [5]. Reasons may include increases in the prevalence of comorbidities including CKD, parallel rises in known precipitants including sepsis, and increasing use of medications or invasive procedures that place patients at increased risk for developing AKI.

Studies focused on the long-term impact of this disease indicate that AKI strongly associates with CKD progression, particularly in severe cases or when superimposed on underlying CKD. Combined with ongoing increases in disease incidence, these observations imply a growing population of survivors of AKI at risk for the development or acceleration of CKD and its complications.

In this chapter, we will examine the bidirectional nature of the interaction between AKI and CKD. Specifically, we will detail how the growing population of patients with CKD may be

especially vulnerable to developing AKI and its complications. In addition, we will discuss emerging literature suggesting that AKI is an important contributor to both the development and progression of CKD. Lastly, we will review recent practice guidelines to the diagnostic approach and management of this disease (Boxes 8.1 and 8.2).

Box 8.1. Relevant Guidelines

1. *KDIGO Guideline*
   Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012;2(Suppl):1–138.
   http://kdigo.org/home/guidelines/acute-kidney-injury/ [2]
2. *European Renal Best Practice Guideline*
   A European Renal Best Practice (ERBP) Position Statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury.
   Nephrol Dial Transplant. 2012;27(12): 4263–72 [7].
   Nephrol Dial Transplant. 2013;28(12): 2940–45 [8].
   http://www.european-renal-best-practice.org/content/position-statement-and-update-kdigo-aki-guidelines-now-available-erbp-website
3. *The Renal Association Guideline*
   Acute Kidney Injury – Final Version (08 March 2011) [9].
   http://www.renal.org/clinical/guidelinessection/AcuteKidneyInjury.aspx
4. *National Institute for Health and Clinical Excellence (NICE) Guideline*
   CG169 Acute kidney injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. Issued: August 2013
   http://publications.nice.org.uk/acute-kidney-injury-cg169 [10]
5. *Canadian Society of Nephrology Guideline:*
   Canadian Society of Nephrology Commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61(5): 673–85 [11]
6. *NKF KDOQI Guideline:*
   KDOQI US Commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61(5):649–72.
   http://www.kidney.org/Professionals/kdoqi/pdf/AKI-Commentary-2013.pdf [12]

Box 8.2. What the Guidelines Say You Should Do in AKI

- The cause of AKI should be determined whenever possible, paying special attention to reversible causes.
- Patients should be risk stratified for AKI according to their susceptibilities and exposures.
- Test patients at increased risk for AKI with measurements of SCr and urine output to detect AKI, with frequency and duration of monitoring based on patient risk and clinical course.
- In the absence of hemorrhagic shock, use isotonic crystalloids rather than colloids as initial management for expansion of intravascular volume.
- Avoid restriction of protein intake for preventing or delaying initiation of RRT.
- Diuretics should not be used to prevent AKI.
- Diuretics should not be used to treat AKI, except in the management of volume overload.
- Low-dose dopamine should not be used to prevent or treat AKI.

Source: Data from Ref. [2]

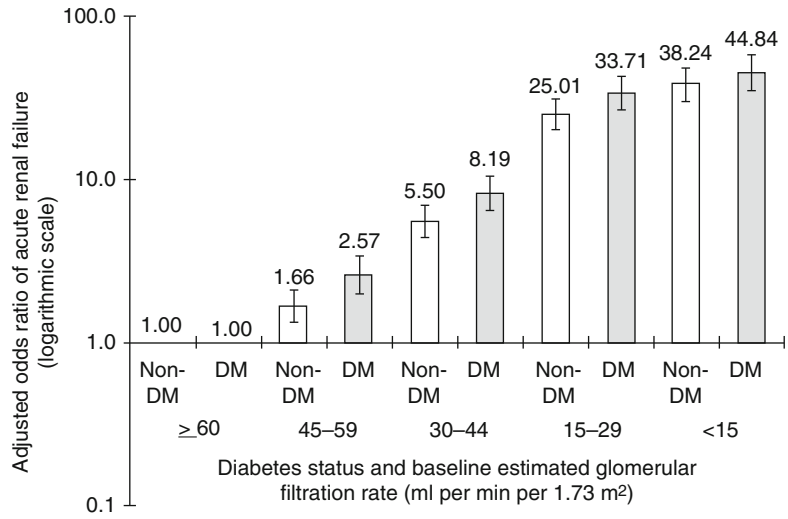


Fig. 8.3 Multivariable association of baseline estimated GFR and dialysis-requiring ARF stratified by the presence or absence of diabetes mellitus (*DM*). Each model adjusted for age, sex, race/ethnicity, diagnosed hypertension, and documented proteinuria (Reprinted with permission from Macmillan Publishers Ltd: Hsu et al. [13])

8.2 CKD as a Risk Factor for AKI

Administrative data have consistently identified CKD as a risk factor for AKI across different clinical settings. However, as many of these early studies used diagnostic coding to identify the occurrence of AKI, concerns over potential biases in detection (e.g., AKI is more likely to be recognized in patients with underlying CKD) prompted additional studies using serum creatinine to define AKI. A population-based study using an integrated health-care database in Northern California observed an adjusted odds of developing dialysis-requiring AKI of up to 20- to 30-fold higher in those with advanced stage III and stage IV CKD compared to non-CKD patients (Fig. 8.3) [13]. Subsequent studies have demonstrated a graded relationship between the severity of CKD and the risk for AKI, indicating that the risk for AKI begins at even earlier stages of CKD [14]. More recently, studies have observed an association between proteinuria and the risk for AKI that appear independent from the effects of eGFR. A recent prospective study of 11,200 in the Atherosclerosis Risk in Communities (ARIC) cohort detected a stepwise increase in risk for AKI with increasing degrees of albuminuria. After adjusting for age, gender, race, cardiovascular risk factors, and categories of eGFR, the ORs for AKI were 1.9 (95 % CI, 1.4–2.6), 2.2 (95 % CI, 1.6–3.0), and 4.8 (95 % CI, 3.2–7.2) for urine albumin-to-creatinine ratio groups of 11–29, 30–299, and ≥300 mg/g, respectively [14]. Another population-based cohort of nearly one million patients in Canada also confirmed a robust association between proteinuria and the risk for hospitalization with AKI, death, and the composite endpoint of doubling of serum creatinine or ESRD. Across all stages of CKD, increasing levels of proteinuria measured by urine dipstick carried an increased adjusted risk for hospitalization for AKI. Even among those with preserved eGFR, mild to heavy proteinuria carried a graded 2.5 (95 % CI: 2.3–2.7)- to 4.4 (95 % CI: 3.7–5.2)-fold risk of hospitalization for AKI (Fig. 8.4) [15].

In summary, these studies reinforce the link between underlying structural or functional impairment of the kidney and the risk for AKI. Whether reducing proteinuria modifies the risk for AKI is an important question that remains to be tested. While the intuitive notion that lower functional reserve in any organ might lower the threshold for injury, the presence of CKD and/or proteinuria remains an important marker to help clinicians identify patients at highest risk for developing AKI. Therefore, we recommend measuring proteinuria and serum creatinine prior to procedures or drug exposures carrying intrinsic risk for AKI (e.g., iodinated contrast procedures)

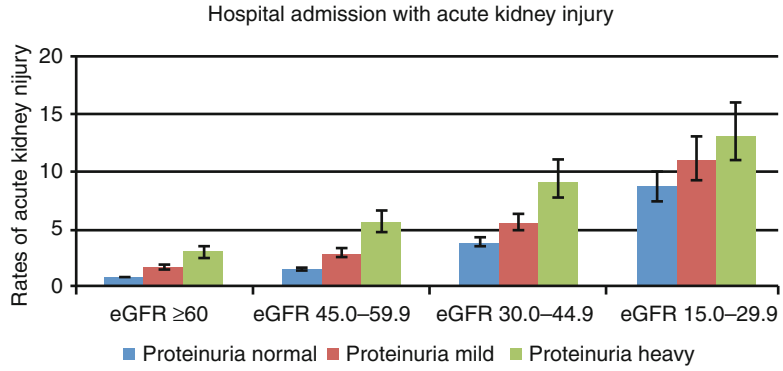


Fig. 8.4 Estimated glomerular filtration rate and proteinuria independently associate with acute kidney injury. Adjusted for means (and frequencies) of covariates for age, sex, aboriginal status, low income, social assistance, and comorbidities (HIV/AIDS, history of cancer, cerebrovascular disease, congestive heart failure, chronic pulmonary disease, dementia, diabetes mellitus, hypertension, metastatic solid tumor, mild liver disease, moderate or severe liver disease, myocardial infarction, paralysis, peptic ulcer disease, peripheral vascular disease, rheumatic disease). In this analysis, dipstick urinalysis was used to classify participants with respect to proteinuria: normal (urine dipstick negative), mild (urine dipstick trace or 1+), or heavy (urine dipstick ≥2+). The tests for linear trend across eGFR categories and across proteinuria categories were all significant at the $p < 0.0001$ level (Data from James et al. [15])

among patients with CKD or other high-risk groups (e.g., elderly, diabetics, hypertension) to better weigh the risks and benefits of a given procedure and to guide use of preventative strategies.

8.3 AKI as a Risk Factor for CKD

Early studies nearly a half-century ago suggested that patients with normal kidney function before severe dialysis-requiring AKI were often able to return to active lives independent of dialysis. However, small but detailed physiologic studies detected subtle decreases in clearance as well as an inability to concentrate and dilute urine among patients whose serum creatinine values appeared to recover. More recently, large observational cohort studies have demonstrated that AKI, particularly when severe, often fails to recover completely, with potential outcomes illustrated in Fig. 8.5. For some patients, there may appear to be a complete or near-complete recovery. In other patients, an incomplete recovery of AKI may occur resulting in the development of incident CKD. Lastly, among those with previous CKD, AKI may serve to accelerate the progressive loss of kidney function over time, yet the mechanisms that lead to decline and potential interventions to attenuate disease progression have not been fully established.

Animal studies have demonstrated that beyond the initial tubular injury and nephron loss, ischemic insults to the kidney also result in endothelial damage to the microvasculature, which has less regenerative capacity than tubules. The loss of vascularity may lead to chronic regional ischemia that promotes downstream hypoxic signaling, inflammation, and fibrosis (Fig. 8.6) [16]. Even after apparent recovery, affected animals can develop proteinuria and are less able to excrete sodium in the urine leading to salt-sensitive hypertension, which may contribute to further loss of kidney function. Further, nephron loss in other experimental models of CKD has also been observed to lead to compensatory adaptations including hyperfiltration that result in glomerular hypertension and cellular proliferation. Whether the latter also occurs following AKI is not clear.

Prospective studies of children who recover from AKI associated with the hemolytic-uremic syndrome (HUS) found survivors were more likely to develop microalbuminuria and lower eGFR values using cystatin C levels relative to a group of control patients during 5 years of

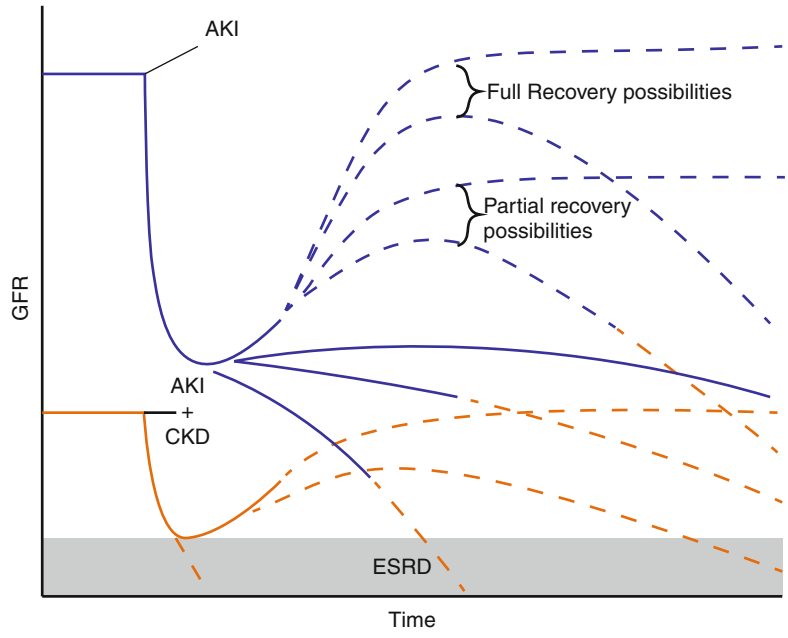


Fig. 8.5 Potential kidney outcomes following AKI

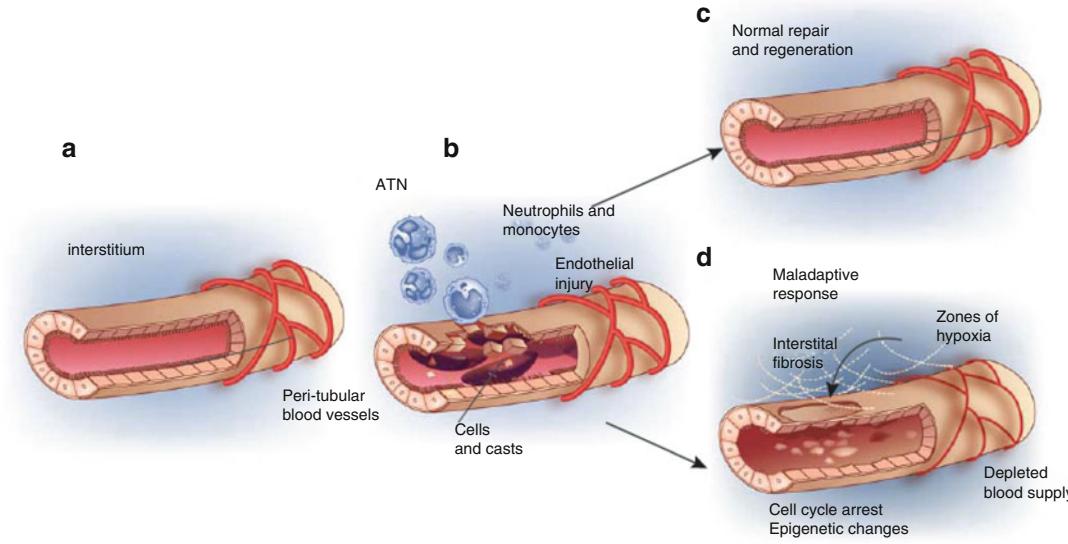


Fig. 8.6 Potential mechanisms of how AKI can lead to irreversible loss of kidney function. Tubule cross section. (**a**) Cross section of normal renal tubule with intact epithelial cells, renal interstitium, and peritubular blood vessels. (**b**) Cross section of renal tubule with acute tubular necrosis (*ATN*) with epithelial cell necrosis, intratubular cast formation, endothelial injury of peritubular blood vessels, and migration of monocytes and macrophages into renal interstitium. (**c**) Cross section of renal tubule after normal repair and regeneration showing restoration of normal renal architecture. (**d**) Cross section of renal tubule after severe episode of AKI, resulting in maladaptive repair. Epithelial cells have evidence of cell cycle arrest and epigenetic changes that favor a fibrosis phenotype. Renal interstitium shows evidence of fibrosis. Post-injury vascular supply is less dense than baseline. The combination of decreased blood supply and fibrosis leads to zones of hypoxia wherein the combination of decreased vascular supply and fibrosis can initiate a vicious cycle leading to ongoing fibrosis (Reprinted with permission from Macmillan Publishers Ltd: Chawla and Kimmel [16])

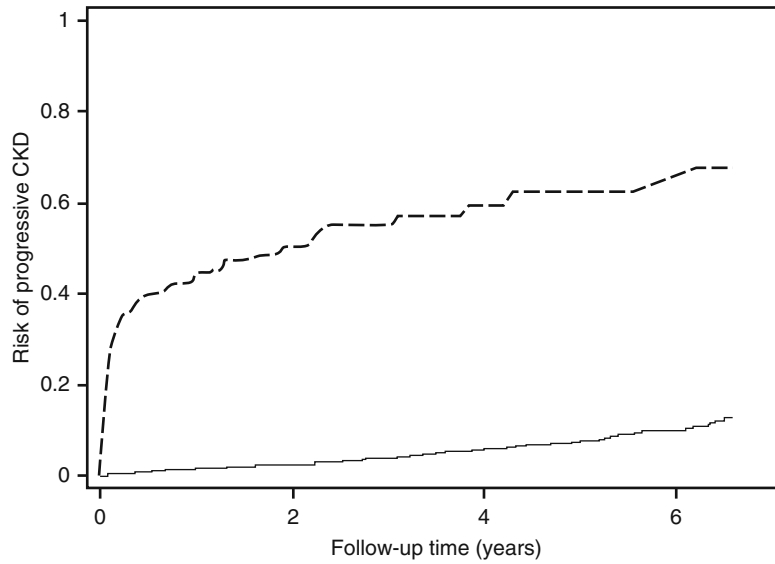


Fig. 8.7 Severe AKI increases the risk of developing advanced kidney disease. Kaplan-Meier curves showing the long-term risk of CKD stage IV or worse among patients with well-preserved kidney function who did (*dashed line*) or did not (*solid line*) suffer and recovered at least partially from dialysis-requiring AKI (Reprinted with permission from Macmillan Publishers Ltd: Lo et al. [19])

follow-up [17]. The extension of these findings to adults has been noted in multiple observational studies [1]. A study using administrative data examined 233,803 hospitalized Medicare beneficiaries found that among those with a discharge diagnosis of AKI, there was a 7 % chance of initiating treatment for ESRD within 2 years of follow-up, with a nearly twofold increase in adjusted risk compared with CKD patients hospitalized without AKI [18]. The likelihood of a patient with CKD experiencing AKI to need treatment for ESRD was 14 %, with an over fourfold adjusted risk compared to CKD patients without an AKI diagnosis.

Subsequent studies anchored by baseline kidney function have found similar results. In a population-based study in Northern California in patients whose eGFR before hospitalization was >45 ml/min/1.73 m^2, patients experiencing dialysis-requiring AKI were 28 times more likely to develop advanced CKD compared to other hospitalized patients without AKI after adjustment and matching for potential confounders (Fig. 8.7) [19]. The risk for incident CKD appears to be increased 1.9-fold even among patients with reversible AKI in whom eGFR returns to within 10 % of their pre-hospitalization baseline [20]. Meta-analyses have estimated pooled adjusted hazard ratios for CKD, ESRD, and mortality following AKI of 8.8 (95 % CI: 3.1–25.5), 3.1(95 % CI: 1.9–5.0), and 2.0 (95 % CI: 1.3–3.1), respectively, compared to hospitalized patients without AKI [1].

Identifying patients at highest risk for developing CKD following AKI has become a high priority. One of the most potent risk factors identified is the severity of AKI [21]. Another potential harbinger of poor outcomes includes the duration of injury. Recent studies in surgical patients found higher long-term mortality rates among those with injury that persists for multiple days, even among those with mild injury [22]. Other risk factors for long-term loss of kidney function following AKI include advancing age; African American race; baseline kidney function; comorbidity burden including the presence of diabetes, hypertension, or congestive heart failure; and serum albumin levels during hospitalization [23].

Lastly, recent attempts have begun to examine the impact of subsequent AKI events on long-term loss of kidney function. Thakar et al. [24] followed a high-risk cohort of 3,679 diabetic patients, 62 % with baseline proteinuria, within an integrated health-care system for the development of stage IV CKD over a mean of 5 years. Despite overall preserved baseline kidney function (mean eGFR 81 ± 26 ml/min/1.73 m^2), fourteen percent of the population experienced an AKI event. Patients experiencing an AKI event were twice as likely to reach stage IV CKD as those who did not

(24.6 % versus 12.9 %, $p < 0.01$). Multivariate Cox regression analysis identified the presence of any AKI to be associated with an adjusted hazard ratio of 3.5 (95 % CI: 2.7–4.6) with each subsequent episode of AKI further doubling that risk (HR 2.02: 95 % CI: 1.78–2.30).

In spite of the accumulating biological and epidemiologic evidence, debate remains over whether the relationship between AKI and the subsequent risk for de novo CKD is a causal one. For example, there is considerable overlap between the risk factors for both CKD and AKI including age, diabetes, hypertension, and cardiovascular disease that can confound this relationship, leading to the hypothesis that AKI is simply a marker for patients who were likely destined to develop CKD. Prospective studies to address these limitations and better identify those likely to have poor longitudinal outcomes have been launched that should shed further light on these issues. In the interim, it is clear that AKI is, at minimum, an important marker for long-term loss of kidney function, particularly among those with preexisting CKD. Therefore, we recommend that an episode of AKI be documented in the electronic medical record and that routine evaluation of all patients with CKD include inquiring about past history of AKI.

8.4 Prevention and Management of AKI in CKD

8.4.1 Before and Early During Hospitalization: Recognizing High-Risk Patients and Situations

As the interaction between AKI and CKD becomes clearer, we will need to improve our understanding of how to optimally care for this growing population. An important first step is for clinicians to recognize how different patients and clinical situations combine to increase the risk for developing AKI in patients with CKD. Among the fastest growing populations experiencing AKI are the elderly, who, like those with CKD, are also less likely to recover and more likely to progress to ESRD following an episode of AKI. Age-related changes in both structure and function of the kidneys and a higher comorbidity burden combine to reduce the threshold for injury. Additionally, these patients are at increased risk for inappropriate drug dosing and polypharmacy that increase the risk of drug interactions and/or nephrotoxicity.

Certain medication classes of proven benefit in the chronic setting can also lower the threshold for AKI during acute illness. For example, the normal response to decreases in kidney perfusion include increases in post-glomerular (i.e., efferent arteriolar) vascular tone, which helps to maintain glomerular perfusion pressure and adequate filtration. However, the increased use of medications in the CKD population, including angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs), blunts the compensatory response that maintains glomerular perfusion pressure. When coupled with diuretics or antihypertensive agents that decrease effective circulating volume or reduce perfusion pressure, the threshold for kidney injury can be lowered. While this risk is presumed to be low in the chronic stable setting, an important component of management is to consider temporary suspension of these medications when the risk for AKI is more dynamic. We recommend educating patients to withhold ACE-I, ARBs, and diuretics during prolonged heat exposure or volume-depleting illnesses such as diarrhea or vomiting, especially if intake of solute and fluids is impaired. Patients should also be especially cautioned to avoid NSAIDs alone or in combination with the aforementioned antihypertensives and/or diuretics. The normal response of the afferent arteriole in states of reduced glomerular perfusion is to dilate in order to maintain glomerular perfusion. However, NSAIDs compromise prostaglandin-mediated dilation of the afferent arterioles during decreased perfusion, which further impairs perfusion to the kidneys in patients with CKD. Health-care providers should have a low threshold for suspending these medications when the risk for AKI is more dynamic such as during hospitalization or before anticipated procedures known to increase risk for

AKI including major surgery or contrast exposure. Communication with procedural teams should be pursued to ensure that risk is minimized (i.e., avoiding contrast load such as ventriculogram or "add-on" vascular studies) and that adequate prophylaxis is given (see Chap. 3 for contrast-induced nephropathy).

Finally, facilitating communication with patients or their surrogates regarding the long-term goals of care *before hospitalization* is a much-needed area for improvement, particularly among frail and elderly patients with CKD. Recent studies have demonstrated that among patients with diminished functional status, such as nursing home residents, nearly two-thirds of patients die within a year of initiating chronic dialysis and premorbid functional status is maintained only in 13 % of patients [25]. Therefore, attempts to ascertain patient goals of care in the context of chronic disease and functional status should occur prior to hospitalization. This will enable patients and physicians with an established relationship to develop a plan of action should hospitalization with AKI occur (e.g., advance directive) and help patients better balance the risk of AKI and its consequences with the benefit of procedures that carry an intrinsic risk for AKI (e.g., major vascular surgery). The possibility of a more conservative approach to care should be presented as a viable option early in the course of conversation, and the joint input of both the patient's primary provider and nephrologist should be sought.

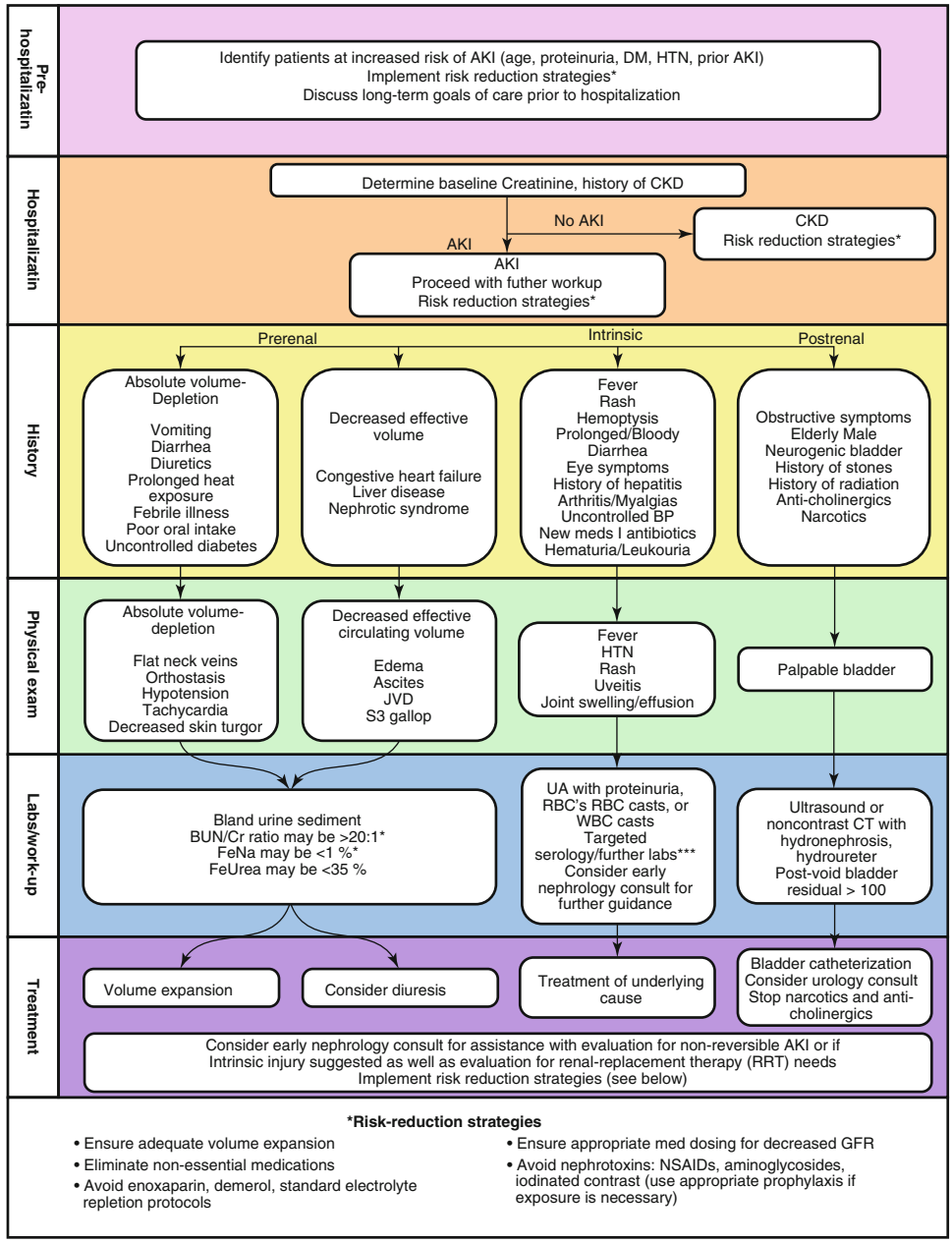
8.4.2 Determining the Time Course and Diagnosis of AKI

A simplified algorithm of the evaluation and treatment of AKI is depicted in Fig. 8.8. In evaluating patients with suspected AKI, effort should be made to determine whether the pattern of kidney injury is acute, acute on chronic, or chronic. This discrimination is important, as some forms of AKI are reversible if the inciting event is removed. Clinicians should elicit a history of CKD including obtaining pre-hospitalization serum creatinine values, if available. Baseline serum creatinine obtained during chronic steady state can provide insight into the acuity of change in kidney function, more accurately gauge the severity of AKI, and provide prognostic information. Any abrupt rise from the baseline creatinine in patients with CKD should prompt evaluations for AKI. Radiographic evidence of small, scarred kidneys would suggest underlying CKD. However, in some cases of CKD, the kidney size may be normal or increased such as in HIV-associated nephropathy, polycystic kidney disease, or infiltrative diseases such as amyloidosis. Additional findings that may suggest underlying CKD include anemia, hyperphosphatemia, hypocalcemia, and hyperparathyroidism.

8.4.3 History, Physical Exam, and the Differential Diagnosis of AKI

Once a diagnosis of AKI has been made, steps should be taken to determine the etiology. Classically, underlying causes are grouped into prerenal, intrinsic, or postrenal categories (Box 8.3). However, many cases of AKI are multifactorial, and multiple contributors should be considered.

Prerenal AKI most often results from impaired perfusion to the kidney and is the most common cause of community-acquired AKI. Early in the course of injury, net filtration is diminished. However, compensatory hemodynamic and hormonal adaptations occur within the kidney that increase the efficiency of filtration and promote sodium and water retention that maintain blood volume and minimize the development of tissue injury *if adequate perfusion can be restored quickly*. Therefore, the diagnosis of prerenal AKI is made retrospectively only after a successful intervention is applied (e.g., creatinine decreases with IV fluid resuscitation). However, deciding which intervention to apply can be challenging as prerenal physiology can be seen in both states of absolute volume depletion (e.g., diarrhea, vomiting, overdiuresis, dehydration, bleeding) and diseases with decreased effective circulating volume (e.g., nephrotic syndrome, liver disease, congestive heart failure) which often present with signs of fluid accumulation (i.e., edema). In patients with underlying CKD, diminished renal reserve



* In CKD, FeN-a may not be <1 % even in pre-renal states. ***CPK. complements, serum and urine protein electrophoresis. ANA. ANCA. anti-GBM Ab

Fig. 8.8 Algorithm for evaluation and treatment of AKI

and blunted ability to adapt to decreased perfusion may lower the threshold for progression to true parenchymal injury, underscoring the importance of a timely diagnosis.

A rapid historical assessment for volume-depleting illness including bleeding, vomiting, diarrhea, febrile illness, infection, or prolonged heat exposure should be elicited. Information on comorbid disease states including poorly controlled diabetes (osmotic diuresis) or those associated with effective arterial volume depletion including congestive heart failure or cirrhosis should also be sought. Additionally, contributing medications should be identified paying particular

attention to recent changes or addition of antihypertensives, diuretics, cathartics, NSAIDs/COX-2 inhibitors, and ACE-I/ARB use. Physical exam should prioritize determining volume status. In cases of absolute depletion of circulating volume, patients may have orthostatic hypotension, flat neck veins, decreased skin turgor, hypotension, or tachycardia. In contrast, patients with decreased effective circulating volume (i.e., cirrhosis or CHF) may have evidence of volume overload including jugular venous distension, S3 gallop, edema, or ascites.

Several laboratory tools have traditionally been used to reflect appropriate tubular response to diminished perfusion, supporting the diagnosis of prerenal azotemia rather than intrinsic causes of AKI during oliguric kidney injury. Among these include a BUN/Cr ratio of >20:1, a fractional excretion of sodium (FeNa) of less than 1 %, or a fractional excretion of urea (FeUrea) of less than 35 % in patients exposed to diuretics. However, the predictive value of these tools in the patient with underlying CKD may be diminished. For example, a lower filtered load of sodium and impaired tubular function may result in a higher FeNa at baseline. Therefore, the predictive value of FeNa levels >1 % for indicating the presence of tubular dysfunction may be less reliable, although a low FeNa of <1 % in the oliguric CKD patient still suggests prerenal azotemia. These caveats place a greater emphasis on history and physical exam findings and other supplemental laboratory data to establish the diagnosis and nature of prerenal AKI (Table 8.2).

A diagnosis of intrinsic kidney injury is made when tissue damage to one or more portions of the kidney (glomerulus, vasculature, tubules, or interstitium) has occurred. A discussion of the vast etiologies of intrinsic AKI is beyond the scope of this chapter; however, ATN is considered to be among the most common injuries in hospitalized patients. Kidney perfusion is estimated to account for 25 % of cardiac output with portions of the tubular epithelium being particularly vulnerable to decreases in perfusion due to high metabolic activity and relative low tissue oxygen content. For this reason, many consider ATN and prerenal azotemia to represent different points on the same spectrum of response to acute ischemia within the kidneys. However, in addition to diminished perfusion, direct tubular injury can result from inflammation from sepsis or nephrotoxic medications including iodinated contrast, NSAIDs, aminoglycosides, and amphotericin (Table 8.3).

Table 8.2 Urinalysis findings in AKI

Normal or hyaline casts	Prerenal azotemia Postrenal/obstruction
Dysmorphic RBCs/RBC casts	Glomerulonephritis Malignant hypertension Thrombotic microangiopathy Vasculitis
WBCs/WBC casts	Glomerulonephritis Acute interstitial nephritis (AIN) Pyelonephritis
"Muddy-brown casts" or pigmented casts	Acute tubular necrosis (ATN) Myoglobinuria Hemoglobinuria
Eosinophiluria	AIN Atheroembolic disease
Crystals	Uric acid Calcium oxalate (can be seen in ethylene glycol ingestion) Calcium phosphate Triple phosphate Cystine Crystal caused by drugs or toxins (indinavir, acyclovir, amoxicillin)

Certain specific diseases can also contribute directly to tubular injury. For example, in some patients with multiple myeloma, monoclonal urinary immunoglobulin light chains (Bence Jones proteins) that are freely filtered can precipitate in the tubular lumen causing intraluminal cast formation and also incite a strong inflammatory reaction that injures tubular epithelia. Clinically, this can mimic ATN, especially since conditions that result in volume depletion can predispose to cast formation. Urinalysis typically shows bland urine sediment and standard urine dipsticks, which detect albumin, do not typically detect light chains. Features

Table 8.3 Drugs associated with AKI

ATN	Antibiotics/antivirals
	Aminoglycosides
	Amphotericin B
	Acyclovir (can also cause crystal formation)
	Indinavir (can also cause crystal formation), tenofovir, cidofovir, adefovir
	Foscarnet
	Pentamidine
	Anti-inflammatory agents
	NSAIDs (including COX-2 inhibitors)
	Immunosuppressive agents
	Cyclosporine
	Tacrolimus
	Chemotherapeutic agents
	Ifosfamide
	Cisplatin
	Organic solvents
	Ethylene glycol (can also cause crystal formation)
	Toluene
	Radiocontrast agents
	Other
	Herbal remedies, acetaminophen
AIN	Antibiotics
	Penicillins
	Cephalosporins
	Sulfamethoxazole
	Ciprofloxacin
	NSAIDs/COX-2 inhibitors
	Loop and thiazide diuretics
	Allopurinol
	Omeprazole
	Phenytoin

that may increase suspicion of myeloma cast nephropathy include ATN without a clear precipitant or out of proportion to the presumed insult in a middle-aged or elderly patient. Accompanying hypercalcemia or anemia, back pain, and/or a history of unexplained CKD should raise suspicion. In these patients, further testing including serum/urine protein electrophoresis, immunofixation, and free light chain assays should be considered. Rhabdomyolysis and gross hemolysis can also cause direct tubular injury due to the release of contents of damaged muscle or red blood cells into the circulation, resulting from trauma, overexertion, autoimmune disease, or associated with medications (e.g., statins). Heme-pigments including myoglobin or hemoglobin are filtered by the glomerulus and degraded with the subsequent release of heme-pigment that can cause direct tubular injury, tubular obstruction, and vasoconstriction. Concurrent volume depletion is an important risk factor in both cases with clinical and laboratory manifestations including decreased urine output, dark urine, elevated creatinine kinase levels (rhabdomyolysis), elevated LDH, low haptoglobin levels (hemolysis), and a urine dipstick that is positive for blood but without obvious red blood cells on microscopy.

Acute interstitial nephritis (AIN) is another subclass of intrinsic kidney injury. AIN is an inflammatory reaction that involves the interstitium of the kidney, the tissue that resides between the tubules. The inflammatory infiltrates generally consist of lymphocytes and monocytes, but plasma cells, eosinophils, and neutrophils may also be present. There is also interstitial edema in sites of inflammatory infiltrate. Medications account for the vast majority of cases of AIN (Table 8.3), with NSAIDs, penicillin antibiotics, and proton-pump inhibitors being common offenders. AIN is also seen rarely as a consequence of infection or systemic disease such as sarcoidosis or Sjögren's syndrome. Physical and laboratory findings consistent with AIN include rash, fever, leukouria, and/or the presence of eosinophils in the blood or urine, though their presence is often variable, as are estimates of their relative and combined diagnostic performance. These observations often make AIN a diagnosis of exclusion. The main treatment of AIN is removal of the offending medication, though steroids may have a limited role. In patients without an obvious cause for AKI, it is important to have a high index of suspicion and a low threshold for discontinuing nonessential medications or using alternatives with less nephrotoxic potential.

Though less common, processes that cause rapid and severe injury to the glomerulus can result in progressive loss of kidney function

over days to weeks and constitute a nephrologic emergency. Acute glomerulonephritis (GN) can be caused by numerous different etiologies including autoimmune and infectious contributions (Box 8.3). History should focus on symptoms of vasculitis including arthritis, rash, hemoptysis, serositis, or risk factors for bloodborne viral infections like hepatitis B, C, and human immunodeficiency virus, or endocarditis. Exam findings of uveitis, arthritis, rash, or embolic phenomenon should increase suspicion for potential for glomerulonephritis. On urinalysis, hematuria and/or proteinuria should prompt examination of the urine sediment for dysmorphic red blood cells or red cell casts (Table 8.2), which suggest glomerulonephritis. If proteinuria is detected, a urine spot protein-to-creatinine ratio (PCR) or 24-h protein excretion should be directly quantified. In general, proteinuria >3.5 g/24 h is considered "nephrotic." If a diagnosis of acute GN is being considered, early nephrology consultation should be considered to guide further serologic testing and to facilitate timely tissue diagnosis and treatment.

The constellation of thrombocytopenia, anemia, and kidney dysfunction, with or without fever and central nervous system (CNS) manifestations, should prompt consideration of thrombotic microangiopathy (TMA). TMA is characterized by microangiopathic hemolytic anemia and thrombocytopenia, with kidney dysfunction and CNS symptoms being variable depending on the degree of platelet thrombosis in the microcirculation. Thrombocytopenia occurs from platelet aggregation in

Box 8.3 AKI: Prerenal, Intrinsic, and Postrenal Causes

Prerenal Causes

Intravascular Volume Depletion

Hemorrhage

Renal losses—aggressive diuresis, osmotic diuresis (hyperglycemia)

Increased insensible losses—sweating, burns

GI losses

"Third spacing"—pancreatitis, rhabdomyolysis

Hypercalcemia (also causes renal vasoconstriction)

Decreased Perfusion

Congestive heart failure

Sepsis

Liver failure

Systemic vasodilation/anaphylaxis

Drugs

Antihypertensives

Diuretics

Anesthetics

Vasopressors

Ergotamine

ACE-I or ARBs—in renal artery stenosis or other causes of hypoperfusion

NSAIDs—during kidney hypoperfusion

Vascular

Renal Artery Stenosis

Intrinsic

Acute Tubular Necrosis

Acute Interstitial Nephritis

Medications

Infections

Small-Vessel Disease

Thrombotic microangiopathy, vasculitis, atheroemboli

Glomerular Disease

Lupus

Anti-GBM disease

Membranoproliferative glomerulonephritis (GN)

Postinfectious GN

Infective endocarditis

IgA nephropathy/Henoch-Schonlein purpura

Tubular Obstruction

Cast nephropathy (multiple myeloma)

Stones or crystals

Postrenal

Bladder outlet obstruction

Calculi

Tumors

Retroperitoneal fibrosis

microcirculation. Hemolytic anemia occurs from mechanical stress and fragmentation of RBCs during transit through narrowed vessels. In addition to thrombocytopenia and anemia, other lab findings include elevated bilirubin, elevated LDH, reticulocytosis, and low haptoglobin. Schistocytes are seen on peripheral smear. Hemolytic-uremic syndrome (HUS) predominantly affects children and is characterized by AKI, often associated with diarrheal illness and usually with minimal or no CNS symptoms. Thrombotic thrombocytopenic purpura (TTP) does occur in adults and generally has CNS involvement with variable kidney involvement. Scleroderma and malignant hypertension can also present with TMA.

Lastly, postrenal AKI refers to obstruction to urine flow within the collecting system (kidney, ureters, bladder, or urethra). Obstruction to urine flow can occur via intraluminal (stones, crystals, urethral stricture) or extraluminal (prostate, retroperitoneal fibrosis) causes. Common causes of postrenal AKI in patients with CKD are prostatic obstruction and defects of bladder emptying such as in neurogenic bladder with long-standing diabetes. Additionally, the use of narcotics or antihistamines (which impair bladder emptying) can be problematic in the elderly. In addition to inquiring about symptoms of urinary difficulty (type and duration) and urinary tract infections or nephrolithiasis, providers should also consider recent exposure to medications that can cause urine crystal formation (intravenous acyclovir or indinavir). In patients with a known history of malignancy, a history of prior radiation to the abdomen or pelvis might suggest the possibility of retroperitoneal fibrosis. It is important to note that the absence of oliguria does *not* rule out significant obstruction. Furthermore, bilateral obstruction is not necessary to have significant worsening of kidney function in patients with CKD, as unilateral obstruction can cause significant decline in kidney function when there is underlying parenchymal disease in the contralateral kidney. In addition to physical exam findings of a distended or palpable bladder, noninvasive renal imaging including ultrasound or noncontrasted CT may reveal a dilated collecting system (i.e., hydronephrosis). Imaging should be obtained whenever there is suspicion of obstruction or if AKI is worsening without an obvious cause. However, imaging may not show evidence of obstruction in patients early in the course of obstruction, with concomitant volume depletion, or those with retroperitoneal fibrosis. A simple measure that can be conducted at the bedside is a bladder scan or post-void urine residual. Urine volume greater than 400 ml on a routine bladder scan or a post-void residual volume of greater than 100 ml should prompt workup and management for outflow obstruction. Prompt relief of outflow obstruction can result in rapid improvement in kidney function if addressed early.

8.4.4 General Management Principles

An exhaustive discussion of specific management strategies across the broad spectrum of AKI is beyond the scope of this chapter. However, once the diagnosis of AKI is made, the search for the underlying cause(s) should be accompanied by a simultaneous assessment for evolving complications. Among these include electrolyte abnormalities (e.g., hyperkalemia, hyperphosphatemia, hypocalcemia), acidosis, volume overload, and signs or symptoms of uremia, such as decline in mental status or pericarditis. We recommend early consultation with a nephrologist in patients with evidence of evolving AKI or evidence of complications, as dialytic therapy may soon be required. Concomitantly, interventions to address potentially reversible causes should be applied. In the absence of obvious volume overload, a trial of volume expansion is often reasonable. While both crystalloid and colloid solutions can be used, isotonic crystalloids are recommended except in cases of hemorrhagic shock [2]. We recommend avoiding starch-based solutions given evolving evidence that they may be associated with the development of AKI. There is no established role for the use of diuretics in *prevention* of AKI. However, if volume overload is thought to be

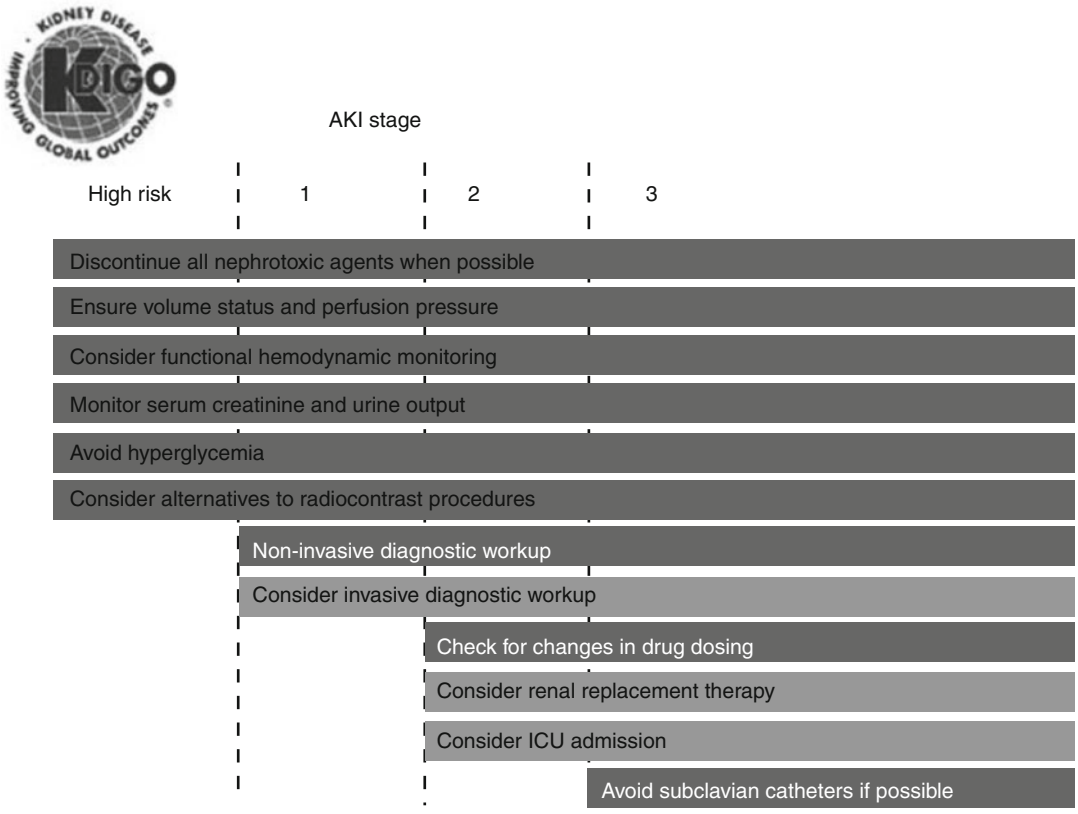


Fig. 8.9 Stage-based management of AKI. *Shading of boxes* indicates priority of action—*solid shading* indicates actions that are equally appropriate at all stages, whereas *graded shading* indicates increasing priority as intensity increases. *AKI* acute kidney injury, *ICU* intensive care unit (Reprinted with permission from Macmillan Publishers Ltd: Kidney Disease: Improving Global Outcomes (KDIGO) [2])

contributing to or complicating the AKI (e.g., congestive heart failure), loop diuretics can be used and are more effective than monotherapy with thiazide diuretics. KDIGO proposes a stage-based approach to the management of AKI, shown in Fig. 8.9. However, we would add that consideration for dose adjustment of drugs as well as the need for renal replacement therapy (RRT) should occur at all stages of AKI and be individualized to each patient. Further, as the optimal care of patients following AKI has not been established, we feel that greater attention for follow-up of patients with AKI shortly after discharge should focus on patients with persistent or moderate to severe injury (KDIGO stages II and III).

It is important to note that estimation of eGFR assumes a "steady state" of glomerular filtration. Thus, eGFR during acute changes in kidney function can misrepresent true GFR. The elevation in creatinine lags behind initial changes in eGFR. Consequently, the trend in creatinine should be considered when interpreting GFR, and if the creatinine trend is increasing, there should be an understanding that the actual GFR is less than the calculated GFR. This is important to keep in mind with medication dosing, particularly with potentially nephrotoxic medications such as vancomycin and aminoglycosides. We would recommend conservative dosing of potentially nephrotoxic medications, cautious use of scheduled dosing in drugs with a narrow therapeutic window, and more frequent measurement of drug levels to guide additional dosing. Some common medications that accumulate with compromised kidney function are listed in Table 8.4.

Table 8.4 Drugs with potentially toxic accumulation in AKI or CKD

Drug	Clinical manifestations of accumulation
Allopurinol	Leukopenia, increased risk for immune-mediated hypersensitivity reaction
Codeine/morphine	Respiratory depression, CNS depression
Propoxyphene	Dysrhythmia
Midazolam	Drowsiness, sedation, apnea
Meperidine	Tremor, agitation, anxiety, myoclonus, seizure
Enoxaparin	Increased risk of bleeding
Succinylcholine	Hyperkalemia

8.4.5 Renal Replacement Therapy (RRT)

Patients whose injury appears progressive or not readily reversible may require dialysis. The optimal timing for initiation of dialysis in patients with AKI is not defined. Currently, the decision to initiate RRT is based on averting or treating complications of AKI including azotemia, hyperkalemia, metabolic acidosis, and volume overload. The process of dialysis itself carries the risk of hypotension and arrhythmia. The anticoagulation process for RRT with heparinization carries bleeding risk, and anticoagulation with regional citrate introduces risk of significant electrolyte abnormalities. Temporary vascular access via catheter for RRT carries risk of bleeding, infection, pneumothorax (with internal jugular catheters), and subsequent central venous stenosis. Balancing the risks and benefits is complex, and we recommend early consultation with a nephrologist to facilitate decision-making.

8.4.6 Special Considerations for the Hospitalized Patient with AKI or CKD

There are some special considerations that should be given to patients with CKD who experience AKI. It is preferable to avoid nephrotoxins including IV contrast dye (e.g., CT with iodinated contrast) in patients with CKD. Additionally, in patients with significantly impaired kidney function (GFR <30 ml/min/1.73 m^2), MRI with gadolinium contrast should be avoided due to the rare but serious potential consequence of nephrogenic systemic fibrosis. Standard electrolyte repletion protocols should be avoided in patients with CKD and with AKI in CKD, as they can result in overcorrection in patients with impaired excretion. In patients with advanced CKD who may need future permanent vascular access for dialysis, an assessment of the patient's nondominant arm should be ascertained. Per KDOQI Guidelines for Vascular Access, permanent vascular access is preferably placed in the patient's nondominant arm to minimize negative impact on quality of life. Full discussion of access planning is beyond the scope of this chapter, but prior central venous access placement resulting in central venous stenosis (e.g., extremity edema or evidence of collateral veins) or presence of cardiac pacemaker device on the nondominant side may preclude vascular access placement in the nondominant arm. In general, we recommend avoiding blood pressure measurement, blood draws, peripheral intravenous access, or peripherally inserted central catheters (PICC) in the arm in which vascular access is planned, as vascular trauma can decrease the likelihood of successful dialysis access placement in the future. Additionally, subclavian central catheters should generally be avoided due to the risk for subsequent central venous stenosis, which can hinder successful creation of arteriovenous fistula or graft placement on the ipsilateral side. Lastly, transfusion of blood products, while often necessary, should be carefully considered in patients who may be eligible for renal transplantation in the future as exposure to and development of preformed antibodies targeting human leukocyte antigen may hinder future organ matching.

8.4.7 Following AKI: At the Time of Discharge and Beyond

As AKI is an important risk factor for both subsequent AKI and accelerated progression of CKD, determining how to best care for these patients

will become increasingly important. Per the KDIGO Clinical Practice Guidelines for Acute Kidney Injury, "patients should be evaluated 3 months after AKI for resolution, new onset or worsening of pre-existing CKD [2]". Recent data have indicated that patients with persistent kidney dysfunction following an AKI event are infrequently seen by nephrologists in the year following AKI. Whether this results in lack of receipt of established standards of care such as timely vascular access for dialysis or transplant referral or risk factor management is unknown. Until we can reliably predict which AKI survivors will develop CKD, we recommend that patients who survive an episode of AKI, particularly if severe or sustained, be followed regularly to assess for early evidence of CKD (i.e., development of hypertension, proteinuria, or reduced eGFR) and to determine if the risk for future injury can be reduced.

8.4.8 Novel Biomarkers in the Diagnosis of AKI

The current gold standard for diagnosis of AKI is based on changes in serum creatinine, making the diagnosis of AKI retrospective. Creatinine alone does not distinguish between prerenal azotemia and true parenchymal damage, nor does it segregate the critical aspects of injury—type of injury, onset, and causation. These limitations have prompted the American Society of Nephrology (ASN) to deem the discovery and standardization of AKI biomarkers with early diagnostic and prognostic potential a *top-priority* research area [26]. Several urine and serum candidate biomarkers have shown promise in specific patient populations with defined cause and timing of injury. Preclinical models have identified these candidate markers as serving a functional (i.e., enzymatic or inflammatory) and/or structural role within renal tubular epithelia, or as low molecular weight proteins filtered by the glomerulus and/or metabolized by healthy tubular epithelia. The native functions of these markers situate them in various intracellular locations or on the plasma membrane. In commonly used animal models of AKI including ischemia-reperfusion or nephrotoxic injury, these markers are actively released or shed in either free or membrane bound form (exosomes) into the urine following tubular damage. Serum/plasma markers, particularly low molecular weight proteins normally filtered by the kidney, have also been studied. Their usefulness in diagnosing and predicting the course of AKI in different patient populations is being investigated. At present, there is insufficient evidence to recommend their routine use in the clinical care of patients.

Conclusion

In summary, the incidence of AKI is increasing and associated with increased morbidity and mortality. AKI is now recognized as a risk factor for progressive CKD. Additionally, patients with CKD are at increased risk for development of AKI due to structural and functional abnormalities, comorbidities, need for invasive procedures, and multiple medications. Patients with rapid progression to ESRD often have courses marked by decline in kidney function due to one or more episodes of AKI. It is important to identify and counsel patients at risk for AKI and to employ risk reduction measures *prior* to the development of AKI. A rapid assessment for reversible causes of AKI should occur, especially in patients with CKD, and treatment aimed at timely optimization of volume and hemodynamic status should be pursued. Early consultation with a nephrologist is indicated if the cause is not immediately clear, evidence of progressive AKI or the complications emerge, or if a tissue diagnosis is required. Finally, patients who experience AKI should be followed for the resolution of AKI and evaluated for development or progression of CKD.

Before You Finish: Practice Pearls for the Clinician

- Check eGFR and proteinuria before exposures to nephrotoxins and high-risk procedures to better identify patients at risk for AKI in whom risk reduction strategies may be helpful.
- Discuss long-term goals of care (including whether to initiate dialysis) *before hospitalization*.
- Obtain pre-hospitalization "baseline" serum creatinine, if possible, to better define kidney function.
- As the rise in creatinine tends to lag behind the inciting injury, focus your search for the underlying cause in the hours to days before creatinine starts to rise.
- The trend in eGFR during evolving or recovering AKI will be more useful for guiding drug dosing than a single eGFR value.
- A high FeNa may not exclude prerenal azotemia in the patient with CKD and AKI.
- Starch-based crystalloid solutions, phosphate-containing cathartics, NSAIDS, and meperidine should be avoided in patients with CKD or AKI.
- Avoid subclavian lines and peripherally inserted central catheters (PICC) to preserve future dialysis access in hospitalized patients with CKD or severe AKI.
- As patients with CKD who experience AKI may be at high risk for progression to ESRD, prior episodes of AKI in the patient's medical history should be documented.
- After an episode of moderate to severe AKI or those where recovery to baseline has not occurred, patients should be evaluated within 3 months for resolution or for new onset or worsening of CKD.

Conflict of Interest Dr. Edward Siew has consulting agreements with Abbvie and Alere, Inc.

References

1. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2011;81(5):442–8.
2. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
3. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. Kidney Int. 2007;73(5):538–46.
4. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol. 2010;21(2):345–52.
5. Hsu CY, McCulloch CE, Fan D, Ordoez JD. Community-based incidence of acute renal failure. Kidney Int. 2007;72(2):208–12.
6. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813–8.
7. Fliser D, Laville M, Covic A, Fouque D, Vanholder R, Juillard L, Van Biesen W' ad-hoc working group of ERBP. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury. Nephrol Dial Transplant. 2012;27(12):4263–72.
8. Jörres A, John S, Lewington A, ter Wee PM, Vanholder R, Van Biesen W, Tattersall J. ad-hoc working group of ERBP. Position statement and update of the KDIGO AKI guidelines now available on ERPB website. Nephrol Dial Transplant. 2013;28(12):2940–45. Available at: http://www.european-renal-best-practice.org/content/position-statement-and-update-kdigo-aki-guidelines-now-available-erbp-website.
9. Lewington A, Kanagasundaram S. The Renal Association Guideline. Acute kidney injury – final version (8 Mar 2011). Available at: http://www.renal.org/clinical/guidelinessection/AcuteKidneyInjury.aspx.
10. National Institute for Health and Clinical Excellence (NICE) guideline CG169 acute kidney injury: prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. Issued: Aug 2013. Available at: http://publications.nice.org.uk/acute-kidney-injury-cg169.
11. James M, Bouchard J, Ho J, Klarenbach S, LaFrance JP, Rigatto C, Wald R, Zappitelli M, Pannu N. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61(5):673–85.

12. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, Tolwani AJ, Waikar SS, Weisbord SD. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis. 2013;61(5):649–72. Available at: http://www.kidney.org/Professionals/kdoqi/pdf/AKI-Commentary-2013.pdf.
13. Hsu CY, Ordonez JD, Chertow GM, Fan D, McCulloch CE, Go AS. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int. 2008;74(1):101–7.
14. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. J Am Soc Nephrol. 2010;21(10):1757–64.
15. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. Lancet. 2010;376(9758):2096–103.
16. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int. 2012;82(5):516–24.
17. Garg AX, Salvadori M, Okell JM, Thiessen-Philbrook HR, Suri RS, Filler G, et al. Albuminuria and estimated GFR 5 years after Escherichia coli O157 hemolytic uremic syndrome: an update. Am J Kidney Dis. 2008;51(3):435–44.
18. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol. 2009;20(1):223–8.
19. Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordo JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int. 2009;76(8):893–9.
20. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle 2nd JE, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int. 2012;81(5):477–85.
21. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. Arch Intern Med. 2011;171(3):226–33.
22. Coca SG, King Jr JT, Rosenthal RA, Perkal MF, Parikh CR. The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. Kidney Int. 2010;78(9):926–33.
23. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int. 2011;79(12):1361–9.
24. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol. 2011;6(11):2567–72.
25. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE. Functional status of elderly adults before and after initiation of dialysis. N Engl J Med. 2009;361(16):1539–47.
26. American Society of Nephrology. American Society of Nephrology Renal Research Report. J Am Soc Nephrol. 2005;16(7):1886–903.