8 Acute Kidney Injury in Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- The incidence of AKI has grown rapidly in recent years.
- CKD and proteinuria are common risk factors for developing AKI.
- Patients with a rapid course to ESKD often have non-linear decline in kidney function marked by AKI.
- Diagnostic tests such as fractional excretion of sodium (FeNa) may be less reliable 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 to resolution and for new onset or worsening of pre-existing CKD.
- Ideally, long-term goals of care (including whether to initiate dialysis) should be discussed *before hospitalization*, particularly among frail and elderly patients with CKD.

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) and consumes 23% of total Medicare expenditures. It is projected that by the year 2030, 16.7% of adults in the US over the age of 30 will have CKD [1]. AKI, particularly when severe, has been recognized as an increasingly common risk factor for CKD progression [2]. AKI is characterized by an abrupt decline in glomerular filtration rate (GFR). The Kidney Disease Improving Global Outcome (KDIGO) Clinical Practice Guideline for Acute Kidney Injury suggests 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 or 1.5 times the baseline value within 7 days, or urine volume less than 0.5 mL/kg/h for at least 6 h (Table 8.1), with increasing severity denoted by incrementally

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Table 8.1 Staging of AKI. Kidney disease improving global outcomes [3]

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

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larger increases in serum creatinine values or the persistence or worsening of oliguria [3]. This change in paradigm has been largely driven by observations showing that even in the absence of overt kidney failure, smaller changes in serum creatinine independently associate with poor clinical outcomes (Fig. 8.1) [4]. Within hospitalized populations, incidence rates for AKI vary by setting, ranging up to 18% in hospitalized patients and up to 57% in ICU patients [5, 6]. Population-based studies within industrialized countries estimate incidence rates for AKI of between 2147 and 5000 cases/million population/year [7].

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 developing countries occurs as a consequence of an acute illness or procedures that either compromise perfusion (e.g., volume-depleting illnesses, acute blood loss,

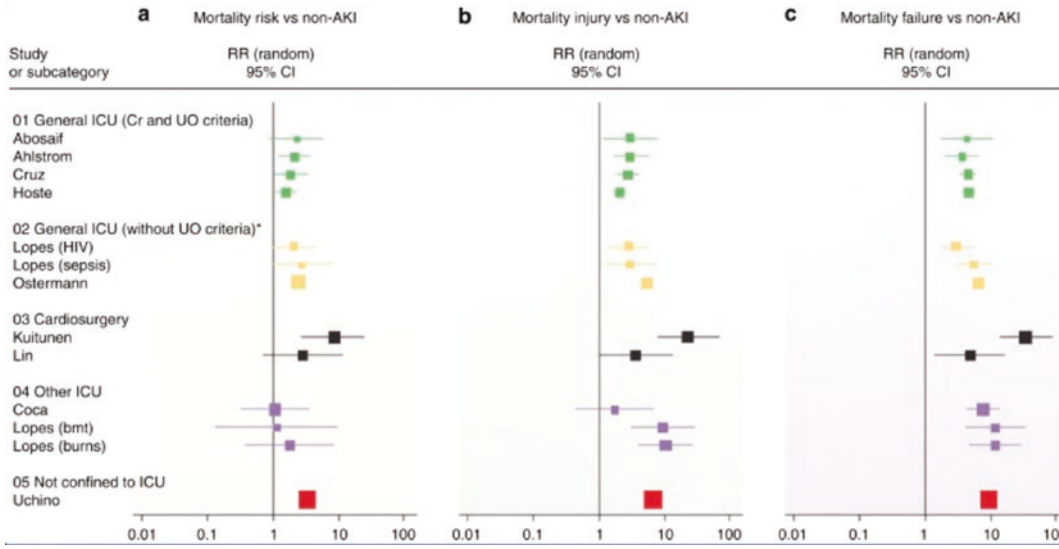

Fig. 8.1 Increased mortality risk associated with AKI extends to milder injury. Systematic review showing consistent increases in mortality risk associated with incrementally larger acute changes in serum creatinine in different acute care settings illustrated by Forrest plot. (**a**) Risk category denoted 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/anuriax12 h (Relative Risk = 6.37). (Reprinted from *Kidney International*; volume 73, issue 5; Ricci Z, Cruz D, Ronco C; The RIFLE criteria and mortality in acute kidney injury: a systematic review; March 2008; pages 538–546, with permission from Elsevier)

Table 8.2 Urinalysis findings in AKI

Normal or hyaline casts	Pre-renal azotemia Post-renal/obstruction
Dysmorphic RBC's/ RBC casts	Glomerulonephritis Malignant hypertension Thrombotic microangiopathy Vasculitis
WBC's/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)

major vascular surgery) and/or stimulate a profound inflammatory response (e.g., sepsis) (Table 8.2). Medications directly toxic to the kidney (e.g., non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast) may also contribute to up to 1/5 of cases [8]. Recent advances in cancer chemotherapies, including immune checkpoint inhibitors and tyrosine kinase inhibitors, have been also associated with AKI. In developing countries, where disease surveillance is not widely implemented, a higher prevalence of diarrheal and infectious-related causes of AKI exist, particularly among children.

8.1.2 Prognosis

AKI is strongly associated with devastating short-term complications with mortality rates up to 56.8% among critically ill patients with severe AKI [5, 8, 9]. Of greater concern are signals arising from both administrative and laboratory databases that the incidence of AKI is expanding rapidly (Fig. 8.2) [7]. Similar growth in nondialysis-requiring AKI, which constitute most cases, has also been observed. There are numerous possible reasons for these increases, including increasing prevalence of comorbidities including CKD, parallel rises in known precipitants including sepsis, increasing use of medications or invasive procedures that place patients at increased risk for developing AKI, and aging populations throughout the world [10]. The latter was illustrated in a study showing that the observed increases in population-based incidences of AKI among a rural United States community from 2006 to 2014 were no longer present after adjusting for age and sex, suggesting that observed increases may be largely related to an increasingly elder population [11].

Recent attention focused on the long-term impact of this disease indicates that AKI strongly associates with CKD progression, particularly in severe cases or when superimposed on underlying CKD, as well as with cardiovascular complications such as heart failure. When taken together with ongoing increases in disease incidence, important implications emerge including a growing population of AKI survivors 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 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.

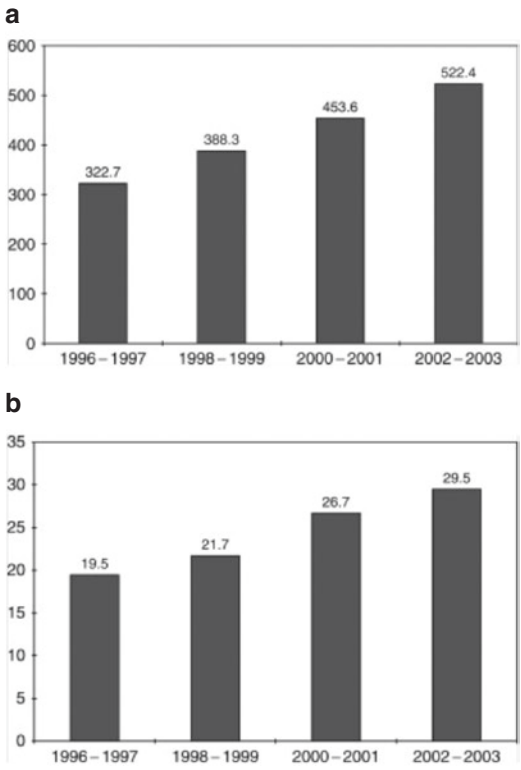

Fig. 8.2 The population incidence of dialysis and non-dialysis requiring AKI in the USA is increasing. (**a**) Community-based incidence rates (per 100,000 person-years) of non-dialysis requiring AKI per year. (**b**) Community-based incidence rates (per 100,000 person-years) of dialysis requiring AKI per year. (Reprinted from Kidney International; volume 72, issue 2; Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM; Community-based incidence of acute renal failure; July 2007; pages 208–212, with permission from Elsevier)

8.2 CKD as a Risk Factor for AKI

Administrative data have identified CKD as a risk factor for AKI. However, as many early studies used diagnostic coding to identify 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 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) [12]. Subsequent studies have demonstrated a graded relationship between the severity of CKD and the risk for AKI, indicating that the increase in observed risk begins at even earlier stages of CKD [13]. Despite the consistency of this data, some concern exists over whether biases in ascertainment may be partially responsible for these observations. Among these include the notion that patients with CKD are more likely to have serum creatinine checked, which increases the likelihood of detecting AKI. In studies that use serum creatinine to define AKI, the same absolute increase in serum creatinine in a patient with CKD represents a smaller overall change in kidney function compared to a patient without CKD, making it easier for patients with CKD to meet diagnostic criteria.

Other markers of kidney disease, such as proteinuria, have also been shown to associate with an increased risk for AKI independent of eGFR. In the Atherosclerosis Risk in Communities (ARIC) cohort, which prospectively followed 11,200 patients, a stepwise increase in risk for AKI was observed 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 to 29 mg/g, 30 to 299 mg/g, and ≥ 300 mg/g, respectively [13]. Another population-based cohort of nearly one million patients in Canada also confirmed an independent association between proteinuria and the risk for hospitalization with AKI, death, and the composite endpoint of doubling of serum creatinine or ESKD. Across all stages of CKD, increasing levels of proteinuria measured by urine dipstick carried an increased adjusted risk for hospitalized 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) [14]. More recently, one study examined the association between proteinuria and post-operative AKI among patients undergoing non-cardiac surgery. After adjustment for kidney function, comorbid conditions, medication use, and intraoperative

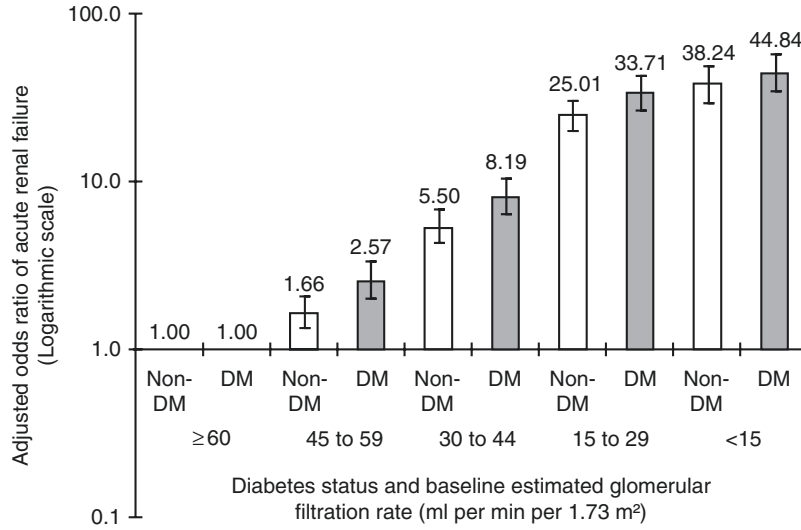

Fig. 8.3 Multivariable association of baseline estimated GFR and dialysis-requiring ARF stratified by the presence or absence of diabetes mellitus (DM). Each model adjusted for age, sex, race/ethnicity, diagnosed hypertension, and documented proteinuria. (Reprinted from Kidney International; volume 72, issue 2; Hsu CY, McCulloch CE, Fan D, Ordonez JD, Chertow GM; Community-based incidence of acute renal failure; July 2007; pages 208–212, with permission from Elsevier)

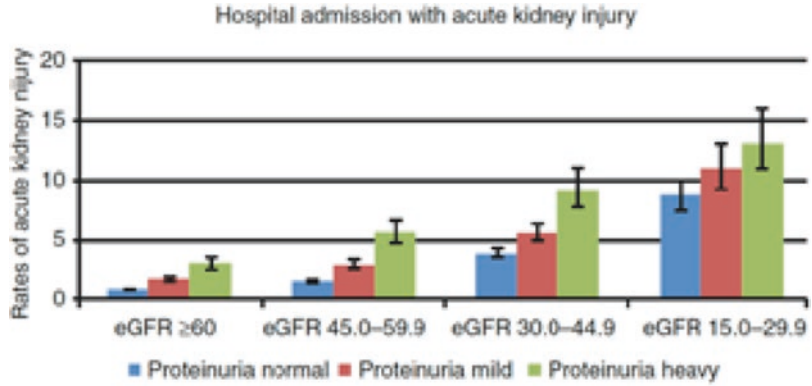

Fig. 8.4 Estimated glomerular filtration rate and proteinuria independently associate with acute kidney injury. Adjusted for means (and frequencies) of covariates for: age, sex, aboriginal status, low income, social assistance, comorbidities (HIV/AIDS, history of cancer, cerebrovascular disease, congestive 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 $p < 0{\cdot}0001$ level. (Data from Lancet 2010 Dec 18;376(9758):2096–103)

hemodynamics, they observed ORs for AKI of 1.14 (95% CI, 0.75–1.73), 1.24 (95% CI, 0.79–1.95), 2.75 (95% CI, 1.74–4.35), and 3.95 (95% CI, 1.62–9.62) for trace, 1+, 2+ and 3+ proteinuria, respectively [15]. A similar trend was observed in a study of United States Veterans undergoing elective inpatient surgery [16].

Chronic kidney disease often co-exists with other comorbid diseases that themselves increase the risk for AKI in this population. Patients with

congestive heart failure, for example, are at risk for AKI that occurs during acute decompensations of the disease itself (i.e., acute cardiorenal syndrome) or exacerbated by its therapy (i.e., diuretics or RAAS inhibitor medications that are used in guideline-directed medical therapy). Cardiovascular disease, including coronary artery disease (CAD), is another common comorbidity that tracks with CKD and is associated with AKI. Patients with CAD are at particular risk of AKI due to contrast exposure (e.g., heart catheterization procedures) and, less commonly, due to atheroembolic disease.

In summary, these studies reinforce the link between both underlying structural or functional impairment of the kidney and the risk for AKI, as well as the susceptibilities conferred by common comorbid conditions and their therapies. Whether reducing proteinuria modifies the risk for AKI remains 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 can 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) to aid in risk stratification.

8.3 AKI as a Risk Factor for CKD

Early studies more than a half-century ago suggested that patients with normal kidney function before a severe AKI event were often able to return to active lives independent of dialysis. However, small but detailed physiologic studies revealed "subclinical" decreases in clearance, as well as an inability to concentrate and dilute urine when measured directly, refuting the notion of AKI being a self-limited event. The potential outcomes of AKI are illustrated in Fig. 8.5. For some patients, there appears to be a complete or near-complete recovery. In others, 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, although 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 have 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) [17]. 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. Furthermore, nephron loss in other experimental models of CKD has also been observed to lead to compensatory adaptations including hyperfiltration in the "remnant kidney" 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 that 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 follow-up [18]. The extension of these findings to adults has been noted in multiple observational studies [2]. One such study used administrative data for 233,803 hospitalized Medicare beneficiaries and found that among those with a discharge diagnosis of AKI, there was a 7% chance of initiating treatment for ESKD within 2 years of follow-up, with a nearly two-fold increase in adjusted risk compared with CKD patients hospitalized without AKI. The likelihood of a patient with CKD experiencing AKI to need treatment for ESKD was 14%, with an over four-fold adjusted risk compared to CKD patients without an AKI diagnosis. The latter is particularly compelling given literature identifying CKD as the *predominant* risk factor for AKI [19].

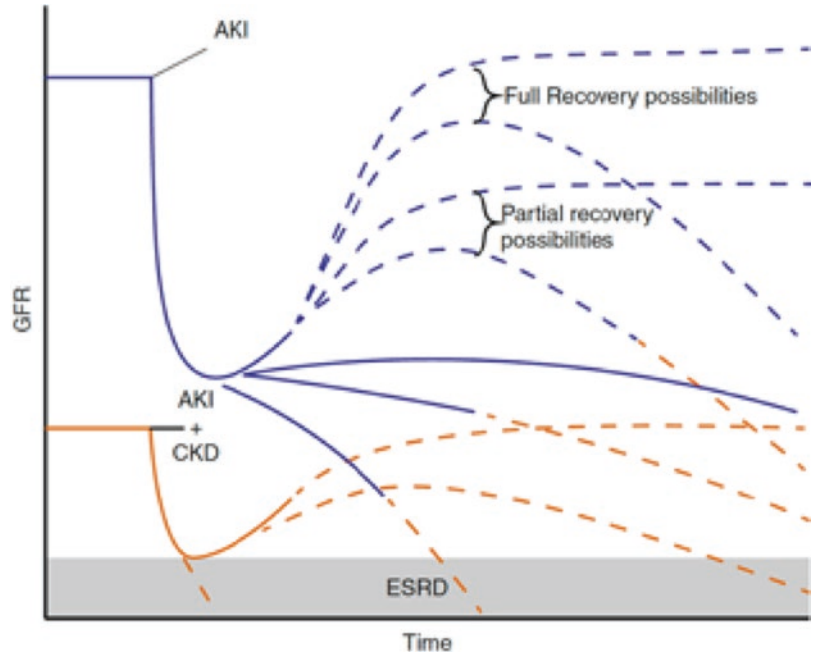

Fig. 8.5 Potential kidney outcomes following AKI

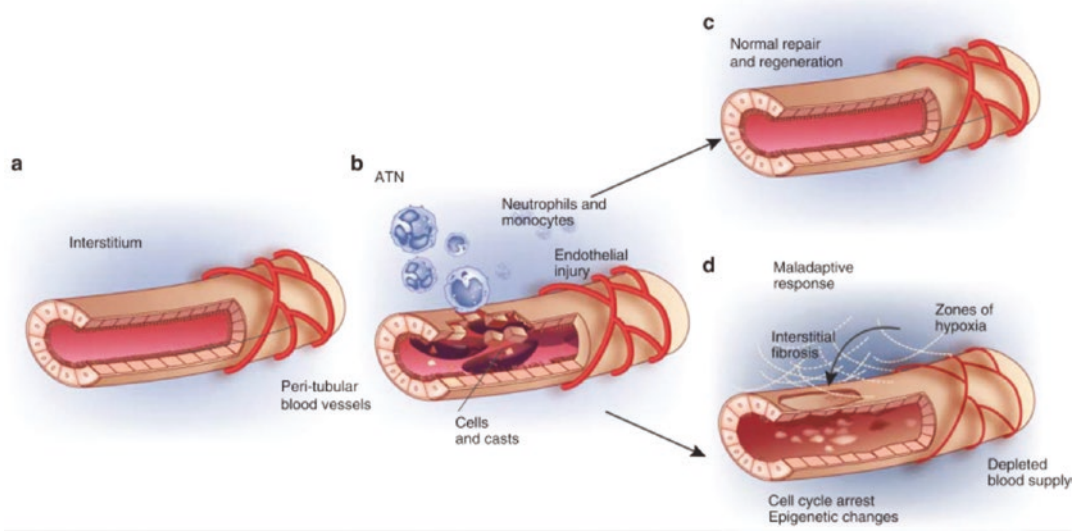

Fig. 8.6 Potential mechanisms of how AKI can lead to irreversible loss of kidney function. Tubule cross-section. (**a**) Cross section of normal renal tubule with intact epithelial cells, renal interstitium, and peri-tubular blood vessels. (**b**) Cross section of renal tubule with acute tubular necrosis (ATN) with epithelial cell necrosis, intra-tubular cast formation, endothelial injury of peri-tubular 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 from *Kidney International*; volume 82, issue 5; Lakhmir CS, Kimmel PL; Acute kidney injury and chronic kidney disease: an integrated clinical syndrome; September 2012; pages 516–524, with permission from Elsevier)

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/1.73m^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) [20]. 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 [21]. Enough data has accumulated to perform meaningful meta-analyses which estimate pooled adjusted hazard ratios for CKD, ESKD, 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 [2]. More recently, the largest multicenter prospective cohort study examined long-term outcomes including kidney disease progression following an episode of AKI among patients who survived at least 3 months after a hospitalization. Among 769 adults with AKI and 769 adults without AKI who were matched on center, baseline CKD status and eGFR, age, comorbidities (diabetes mellitus and cardiovascular disease), and treatment in the ICU, AKI was associated with an increased risk of both incident CKD and progressive CKD (adjusted hazard ratio for incident CKD 3.98, 95% CI 2.51–6.31; aHR for CKD progression 2.37, 95% CI 1.28–4.39) [22].

Building upon this literature, recent efforts have focused on identifying patients at highest risk for developing CKD following AKI. Several studies have demonstrated a graded relationship between AKI severity (as measured by change in serum creatinine) and the risk for incident and progressive CKD [23]. Another potential harbinger of poor outcomes includes the duration of injury. Studies in surgical patients found that higher long-term mortality rates among those with injury that persists for multiple days, even among those with mild

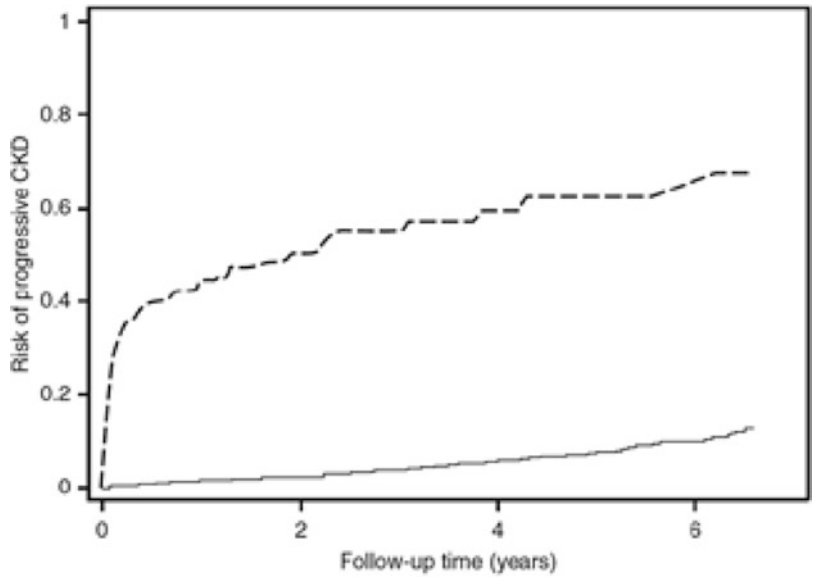

Fig. 8.7 Severe AKI increases the risk of developing advanced kidney disease. Kaplan-Meier Curves showing the long-term risk of KDOQI Stage 4 or worse kidney disease among patients with well-preserved kidney function who did (dashed line) or did not (solid line) suffer and recovered at least partially from dialysis-requiring AKI. (Reprinted from *Kidney International*; volume 76, issue 8; Lo LJ, Go AS, Chertow GM, et al.; Dialysis-required acute renal failure increases the risk of progressive chronic kidney disease; October 2009; pages 893–899, with permission from Elsevier)

injury, and were more prognostic than injury severity alone [24]. More recent studies in hospitalized and cardiac surgery patients have shown similar findings. A large retrospective study of hospitalized patients showed a dose-dependent association between duration of AKI with incident CKD at 1 year [25], while a study of patients undergoing elective cardiac surgery found that duration of AKI lasting >3 days had an adjusted odds ratio of 13.5 (95% CI 4.2–43.7) for incident CKD at 1 year [26]. Non-recovery from AKI may also be predictive of CKD progression. In a multivariable model predicting risk of progression to advanced CKD among survivors of AKI, serum creatinine at hospital discharge and AKI severity were major drivers of risk (C statistic for full model 0.81, 95% CI 0.75–0.86) [27]. 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, HTN, or CHF, and serum albumin levels during hospitalization [28]. Proteinuria following AKI has also been shown to be a predictor of long-term kidney disease. In a study of patients with AKI sustained during a hospitalization, higher levels of albuminuria measured at 3 months after hospital discharge were associated with increased risk of progressive chronic kidney disease, defined as a halving of estimated GFR or end-stage kidney disease [29].

Lastly, the majority of studies have characterized the impact of a discrete episode of AKI on disease progression. However, recent attempts have also begun to examine the impact of subsequent AKI events on long-term loss of kidney function. Thakar et al. [30] followed a high-risk cohort of 3679 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), 14% of the population experienced an AKI event, with nearly one-third of this group experiencing multiple events. Patients experiencing an AKI event were twice as likely to reach stage IV CKD as those who did not (24.6% vs. 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). Retrospective studies have identified factors that may increase an individual's risk for recurrent AKI, including demographics (older age, black race, Hispanic ethnicity), comorbid conditions (congestive heart failure, diabetes, liver disease, and cancer), acute events (decompensated liver disease, acute coronary syndrome, volume-depleting events), and more severe illness at index hospitalization [31, 32]. Renal functional reserve (RFR), which refers to the kidney's ability to increase its filtration rate in response to a stimulus, is a topic of ongoing investigation and a factor that appears to be associated with risk of AKI. RFR is measured as the difference between baseline GFR and GFR measured after a protein load. Assessment of RFR may more accurately capture the degree of structural injury following AKI in patients with normal GFR (i.e., subclinical injury). Diminished RFR has also been observed in patients with CKD. Recent studies have demonstrated that lower RFR are associated with risk of AKI, as was shown in a study of patients undergoing cardiac surgery who had RFR measured pre-operatively; in that study, pre-operative RFR predicted post-operative AKI with an area under the receiver operator curve of 0.83 (95% CI, 0.70–0.96), and patients with a RFR $\leq$ 15 mL/min/1.73m^2 were 11.8 times more likely to experience AKI [33]. RFR measurement is not used in routine clinical practice at present, and remains an area of active investigation.

With biological and epidemiologic evidence supporting an independent association between AKI and incident CKD, research efforts over the past decade have explored potential mechanisms by which AKI may lead to new or progressive CKD. Preclinical studies have implicated maladaptive repair processes after AKI which may promote interstitial fibrosis through a number of mechanisms. Tubular injury can result in interstitial fibrosis through secretion of profibrotic fac-

tors and tubular mitochondrial dysfunction [34]. AKI can also cause a reduction in capillary density in affected tissue (microvascular rarefaction) which may promote interstitial fibrosis through renal hypoxia [35]. Identification of these biochemical pathways of progression holds promise for possible targets of therapy, however this work remains nascent [36]. Regardless, it is clear that AKI is an important marker for long-term loss of kidney function, particularly among those with pre-existing CKD. Therefore, we recommend that an episode of AKI be documented in the medical history portion of the electronic medical record, and that the 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, improved understanding of how to optimally care for this growing population will be needed. An important first step is for clinicians to recognize the patients and situations that combine to increase the risk for developing AKI in patients with CKD. In addition to patients with CKD, other patients at risk of developing AKI include patients with diabetes, hypertension, heart failure, and African American race. Among the fastest growing populations experiencing AKI include the elderly, who like those with CKD are also less likely to recover and more likely to progress to ESKD following AKI. Age-related changes in both structure and function of the kidneys in this population and a higher comorbidity burden combine to reduce the threshold for injury in response to abrupt changes in renal perfusion. 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 postglomerular (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. This risk is particularly relevant in patients with heart failure, for whom increasingly potent blockade of the renin-angiotensin system coupled with aggressive diuresis as part of evolving guideline-directed medical therapy may lower the threshould for AKI. Careful stepwise initation and titration of these medications may be warranted in patients with underlying CKD. Furthermore, temporary suspension of these medications during AKI or when the risk for AKI is high (such as during acute illness) may be prudent. In these so-called sick-day protocols patients are instructed to withhold ACE-I, ARBs, and diuretics during volume-depleting illnesses such as diarrhea or vomiting. The evidence to support the widespread adoption of such protocols has been mixed. A pooled analysis of three randomized clinical trials that examined similar protocols in which specific medications are temporarily withheld during illness or a radiologic or surgical procedure found a nearly 50% increased risk of AKI among those who continued the meds compared with those who held them as part of the sick-day protocol, however the observed effect was not statistically significant (RR

1.48, 95% CI 0.84–2.60) [37]. The effectiveness of sick-day protocols in reducing AKI may also be limited by insufficient understanding by patients. Illustrating this point, a small study of 20 volunteers with stage 3–5 CKD assessed the usability of the sick-day protocol used by the National Health System in Scotland. The volunteers were educated about the protocol and provided mock medication bottles, and were then asked which (if any) medications should be held in four different clinical scenarios. Of the 20 study participants, only one individual was able to identify the correct medications to hold in each of the four scenarios [38]. An ongoing clinical trial examining this topic is being completed at the time of this writing and may provide better guidance. We do recommend that patients with CKD be cautioned to avoid NSAIDs in combination with the aforementioned antihypertensives and/or diuretics as the latter compromise prostaglandin-mediated dilation of the afferent arterioles during decreased perfusion, which may make patients with CKD more vulnearable. Healthcare 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., minimizing contrast loads) 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. 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 [39]. 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 potential AKI 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 a patient 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 evaluation 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 diabetic nephropathy, HIV-associated nephropathy, polycystic kidney disease, or infiltrative diseases such as amyloidosis. Additional findings that may suggest underlying CKD include anemia, hyperphosphatemia, hypocalcemia, hyperparathyroidism, and neuropathy.

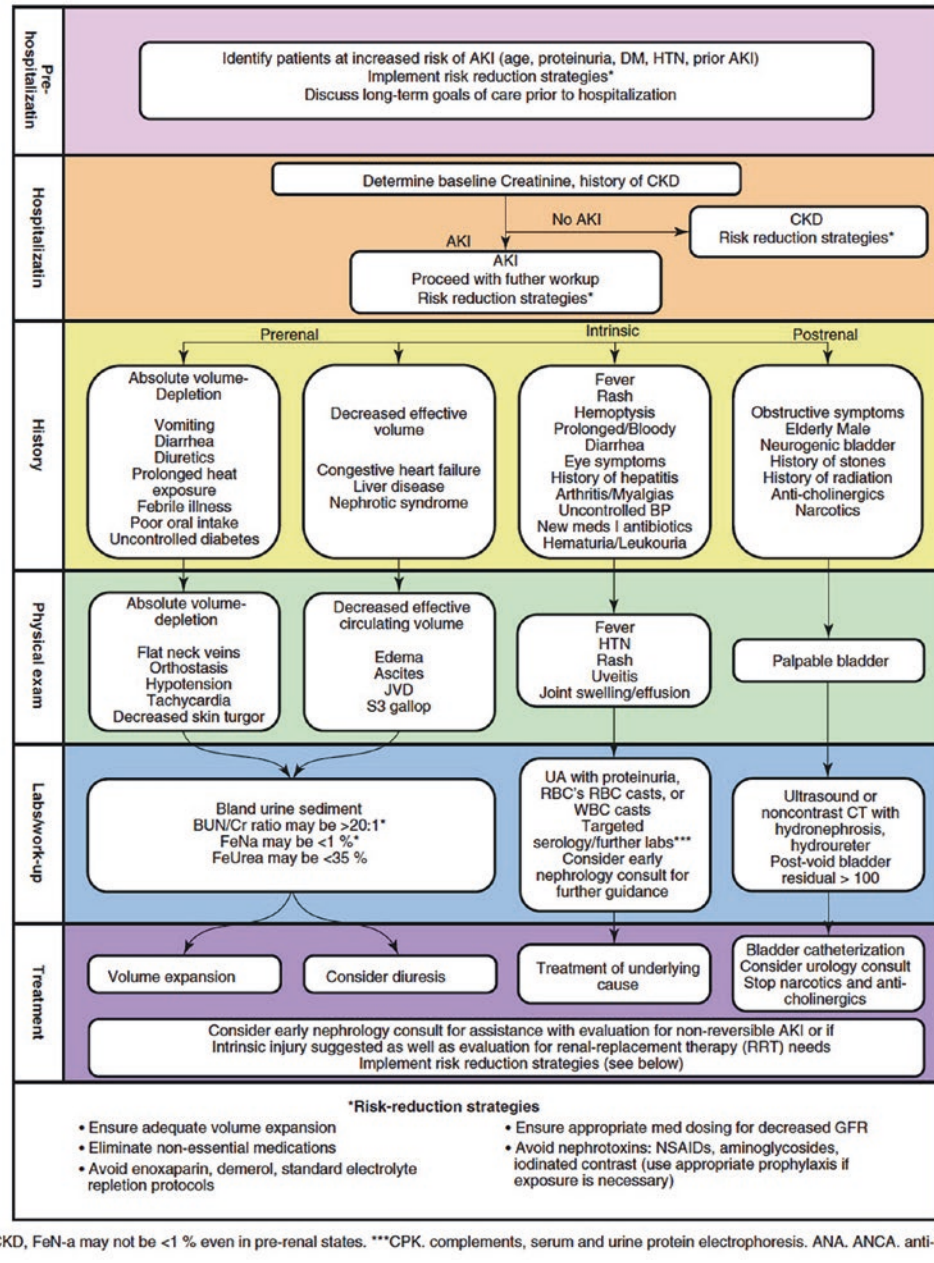

Fig. 8.8 Algorithm for evaluation and treatment of AKI

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 pre-renal, intrinsic, or post-renal categories (Table 8.2). However, many cases of AKI are multifactorial and multiple contributors should be considered.

Pre-renal 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 pre-renal AKI is made after a successful intervention is applied (e.g., creatinine decreases with IV fluid resuscitation). However, deciding which intervention to apply can be challenging as pre-renal 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 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/ARB use. Physical exam should prioritize determining volume status. In patients with 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 such as patients with 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 pre-renal 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 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 pre-renal 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 pre-renal AKI listed in Text Box 8.1.

A diagnosis of intrinsic renal injury is made when tissue damage to one or more portions of the kidney (glomerulus, vasculature, tubules, or interstitium) has occurred. While a discussion of the vast etiologies of intrinsic AKI is beyond the scope of this chapter, 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,

Box 8.1 AKI: Pre-Renal, Intrinsic, and Post-Renal Causes

Pre-Renal 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 ARB's—in renal artery stenosis or other causes of hypoperfusion
- NSAID's—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)
- Post-infectious GN
- Infective endocarditis
- IgA nephropathy/Henoch-Schonlein purpura

Tubular obstruction
- Cast nephropathy (multiple myeloma)
- Stones or crystals

Post-Renal
- Bladder outlet obstruction
- Calculi
- Tumors
- Retroperitoneal fibrosis

many consider ATN and pre-renal 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). Novel anticancer therapies developed over the past two decades, including molecularly targeted agents (small molecule tyrosine kinase inhibitors and monoclonal antibodies) and immune checkpoint inhibitors (ICIs), have also been associated with kidney complications including electrolyte abnormalities and AKI. The incidence of AKI associated with these therapies ranges from 2 to 7% depending on the agent [40–43]. Direct nephrotoxicity from these agents can occur by a number of mechanisms. Intraglomerular thrombotic microangiopathy (TMA) is a rare but serious complication that is seen with agents targeting vascular endothelial growth factor (e.g., bevacizumab and lenvatinib). Patients with AKI caused by TMA typically present with proteinuria and hypertension. Drug withdrawal or dose reduction is often adequate therapy, though some patients may require eculizumab, plasmapheresis, or rituximab to restore renal function [44, 45]. Biopsy series suggest acute tubulointerstitial nephritis (ATIN) is a common form of kidney injury in patients treated with an ICI [41]. Risk factors for ATIN include eGFR <60 and concurrent proton-pump inhibitor use [46]. Various case series and case reports suggest that treatment

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
	Chemotherapeutic agents (cause acute tubulointerstitial nephritis)
	Tyrosine kinase inhibitors
	Immune checkpoint inhibitors
	Loop and thiazide diuretics
	Allopurinol
	Omeprazole
	Phenytoin

with glucocorticoids and drug discontinuation are effective in achieving at least partial kidney recovery, with a recurrence rate after therapy reinitiation of 16% [46, 47]. Glomerular diseases (most commonly minimal change disease, focal-segmental glomerulonephritis, and membranous nephropathy) have also been associated with these novel agents and typically present with nephrotic syndrome. Glucocorticoids and drug discontinuation generally lead to at least partial recovery in most patients [48–51].

Certain 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 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 typically detect albumin and not light chains. Features 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 (rhadomyolysis), 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. Rarely, AIN can be seen 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 estimates of their relative and combined diagnostic performance are highly variable. The main treatment of AIN is removal of the offending medication, though steroids may have a limited role when initiated early.

Though less common, processes that cause rapid and severe injury to the glomerulus can result progressive loss of kidney function over days to weeks and constitute a nephrologic emergency. Acute glomerulonephritis (GN) can be caused by numerous etiologies including autoimmune diseases and infections (Table 8.2). History should focus on symptoms of vasculitis including arthritis, rash, hemoptysis, serositis or risk factors for blood-borne 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 8.4), which suggest glomerulonephritis. If proteinuria is detected, a urine spot protein-to-creatinine ratio (PCR) or 24-h 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.

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

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 other end-organ manifestations such as kidney dysfunction and CNS symptoms being variable depending on the degree of platelet thrombosis in the microcirculation. Thrombocytopenia occurs from platelet aggregation in microcirculation. Hemolytic anemia occurs from mechanical stress and fragmentation of RBC's 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, post-renal 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 post-renal AKI in patients with CKD are prostatic obstruction and defects of bladder emptying such as in neurogenic bladder in patients with long-standing diabetes. Additionally, the use of narcotics or anti-histamines (which impair bladder emptying), can be particularly problematic in the elderly. In addition to inquiring about symptoms of urinary difficulty (type and duration) and history of uri-

nary 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, non-invasive renal imaging including ultrasound or non-contrasted 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 early in the course of obstruction in patients with concomitant volume depletion or 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 work-up 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 abbreviated summary of AKI treatment guidelines is provided in Text Box 10.2. 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 complications of AKI or progressively worsening AKI, as dialytic therapy may 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 [3]. Balanced crystalloid solutions (e.g., lactated ringers) may be superior to non-balanced crystalloids (e.g., normal saline), as data from recent randomized clinical trials of patients in emergency department and ICU settings have observed improved outcomes (including lower mortality, less renal replacement therapy and persistent kidney dysfunction, and hospital-free days) with use of balanced crystalloids compared with normal saline [52]. Starch-based solutions should be avoided 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 contributing to or complicating the AKI (e.g., congestive heart failure), loop diuretics can be used and are preferred over monotherapy with thiazide diuretics, as the latter are less efficacious in patients with diminished GFR. 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 and assessment of the need for renal replacement therapy (RRT) should occur at all stages of AKI and be individualized to each patient. Furthermore, 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 injury or among those with moderate to severe injury (KDIGO Stages II and III).

Box 8.2 Abbreviated Summary of Guidelines for Treatment of AKI [3]

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 with the aim of 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

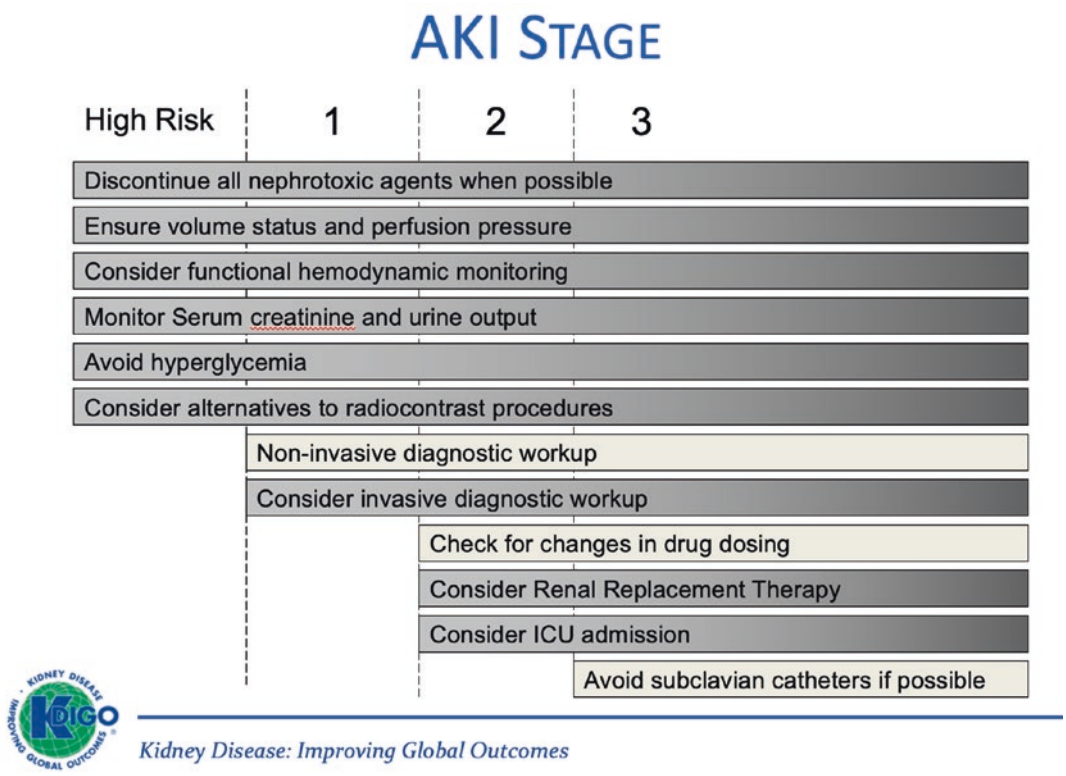

Fig. 8.9 Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. *AKI* acute kidney injury, *ICU* intensive-care unit. (Reprinted from *Kidney International Supplements*; Volume 2, Issue 1; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group; KDIGO Clinical Practice Guideline for Acute Kidney Injury; 2012; pages 1–138; with permission from Elsevier)

It is important to note that the estimation eGFR assumes a "steady state" of glomerular filtration. However, elevation of creatinine lags behind the initial decrease in GFR and the calculated eGFR is not necessarily an accurate reflection of true GFR in patients with AKI and dynamic changes in kidney function. 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 evaluation of measurable drug levels to guide additional dosing. Some common medications that accumulate with compromised kidney function are listed in Table 8.4.

8.4.5 Renal Replacement Therapy (RRT)

Patients whose injury appears progressive or not readily reversible may require dialysis. The decision to initiate RRT is generally based on averting or treating complications of AKI including azotemia, hyperkalemia, metabolic acidosis, and volume overload. Despite its critical role in managing severe AKI, RRT is not devoid of risk. 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 risk of subsequent central venous stenosis. There is also a concern that the effects of RRT may delay recovery of renal function and contribute to the progression of CKD, though this has yet to be proven. Given these considerations, the optimal timing to initiate dialysis has been unclear. Over the past decade this topic has been studied in multiple randomized clinical trials comparing early versus delayed dialysis initation strategies. The earliest of these included two RCTs (AKIKI and ELAIN), which compared overall survival in critically ill patients with severe AKI who were randomized to early versus delayed dialysis initiation strategies. The two studies had conflicting findings, with AKIKI observing no survival benefit at 60 days with the early initiation strategy, while ELAIN observed a reduced mortality at 90 days with early initiation [53, 54]. Notably, nearly half of patients in the delayed arm of the AKIKI trial did not start RRT, and there were twice the rate of catheter-associated bloodstream infections in the early arm.

Given the discrepant findings of AKIKI and ELAIN, the IDEAL-ICU study similarly compared early and delayed initiation of RRT in patients septic shock and severe AKI. IDEAL-ICU was stopped early for futility after showing no significant difference in 90-day mortality. Most recently, STARRT-AKI, a large multinational trial randomized over 3000 patients with severe AKI (defined as KDIGO stage 2 or 3 AKI) to an accelerated (within 12 h of meeting eligibility criteria) or standard strategy (dialysis for specific indication or if AKI duration exceeding 72 h). Consistent with the findings of AKIKI and IDEAL-ICU, STARRT-AKI found no significant difference in 90 day mortality observed with early initiation [55]. With the benefit of early initiation of dialysis not having been consistently demonstrated, we generally favor a delayed approach in initiating RRT for AKI that is guided by specific clinical indications.

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 nephrotoxic exposures 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 when possible due to the rare but serious potential consequence of nephrogenic systemic fibrosis (NSF). Newer gadolinium agents may have a better safety profile, though it is unclear if the lower incidence of NSF observed since these agents have come into use is due to lower risk of the agents itself or the more judicious use of the agents in individuals with kidney disease [56]. Standard electrolyte repletion protocols should be avoided in patients with CKD and with AKI in CKD, as the "standard repletion" protocols for potassium, magnesium and phosphorus can result in overcorrection in patients with impaired excretion. In patients with advanced CKD who may need permanent vascular access for dialysis in the near future, an assessment of the patient's dominant arm should be ascertained, and the non-dominant arm should be avoided for blood pressure measurement, blood draws, and peripherally inserted central venous catheters. Additionally, subclavian central catheters should be avoided due to the risk for subsequent central venous stenosis, which can hinder successful creation of arterioveneous 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 data accumulate indicating that AKI is an important risk factor for both subsequent AKI and accelerated progression of CKD, determining how to best care for these patients will depend on identifying potential care processes that can reduce the risk for further injury. 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" [3]. However, studies have indicated that patients with persistent kidney dysfunction following an AKI event are infrequently seen by nephrologists in the year following AKI and may even be unaware of having had AKI. A recent study finding that among survivors of stage 2–3 AKI, a majority were unaware of that diagnosis at hospital discharge [57]. 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. We recommend that patients who survive an episode of AKI, particularly if severe, be followed regularly to assess for early evidence of CKD (i.e., development of hypertension, proteinuria, or reduced GFR). Post-AKI proteinuria in particular has been shown to be a valuable predictor of CKD progression among patients who survive AKI, with a prospective study of AKI survivors found that the risk of kidney disease progression increased by over 50% for every doubling of post-AKI urine albumin-creatinine ratio (HR 1.53 for each doubling, 95% CI 1.45–1.62) [58]. Follow-up care after AKI also provides the opportunity for a careful appraisal of a patient's medications to ensure appropriate dosing, assess nephrotoxin exposures, and consider resuming nephro- and cardioprotective medications such as ACE-I and ARB. The importance of medication reconciliation after an episode of AKI was illustrated in a recent study that found an increased risk of hypoglycemia after hospital discharge in diabetic patients with AKI compared with matched diabetic patients who did not have AKI (HR 1.27, 95% CI 1.22–1.33); the risk was even higher among patients with non-recovery of kidney function after AKI (HR 1.48, 95% CI 1.36–1.60) [59]. Finally, survivors of AKI appear to be at increased risk of cardiovascular disease. In a systematic review and meta-analysis of cohort studies of adults with and without AKI, individuals with AKI had an 86% and 38% increased risk of cardiovascular mortality and major cardiovascular events, respectively (RR 1.86; 95% CI, 1.72–2.01 and RR 1.38; 95%

CI, 1.23–1.55) [60]. A subsequent prospective cohort study that examined outcomes among survivors of AKI compared with matched patients without AKI found that AKI was associated with increased risk of heart failure events, which was attenuated after adjusting for residual kidney function and proteinuria at 3 months following hospital discharge [22]. As cardioprotective medications are often suspended around the time of AKI, and with CKD a potent cardiovascular risk factor, it is important that careful reinitiation of these medications be considered after AKI has resolved.

8.4.8 Novel Biomarkers in the Diagnosis of AKI

The current gold standard for diagnosis of AKI relies on changes in serum creatinine, which provides a retrospective surrogate measure of GFR, but provides little to no additional phenotyping. Creatinine alone does not distinguish between pre-renal azotemia and true parenchymal damage, nor does it characterize the critical aspects of injury—type of injury, onset, or etiology. These limitations 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 [61]. In the time since, several urine and serum candidate biomarkers have shown promise in specified patient populations with defined use cases. The rationale for their use derives from preclinical identification of candidate markers serving a functional (i.e., enzymatic or inflammatory) and/or structural role within renal tubular epithelia, or as low molecular weight proteins normally filtered through by the glomerulus and/or metabolized by healthy tubular epithelia. The native functions of these markers indicate their various locations (i.e., intracellular or on the plasma membrane). In commonly used animal models of AKI including ischemia-reperfusion or nephrotoxic injury, active release or shedding of these markers in either free or membrane bound form (exosomes) into the urine following tubular damage has prompted testing in analogous settings of human injury such as cardiopulmonary bypass. Serum/plasma markers, particularly low molecular weight proteins normally filtered by the kidney have also been studied. Early applications of novel biomarkers have included clinical trials, where they have been used in enrollment criteria to enrich study populations, as well as AKI phenotyping studies, though validation of their strength as indicators of specific injury types remains ongoing. Recently, the acute dialysis quality initiative (ADQI) suggesed a potential role of novel biomarkers in combination with serum creatinine to differentiate types of AKI by distinguishing functional changes (elevation in serum creatinine) from evidence of structural damage (biomarker elevation) [62]. These AKI categories provide substages of KDIGO stages of AKI, including stage 1S (“subclinical” AKI: creatinine negative, biomarker positive), stage 1A: (“pre-renal azotemia”: creatinine positive, biomarker negative), and stage 1B (“intrinsic AKI”: creatinine positive, biomarker positive). The strength of this recommendation was condional, indicating that further research is needed to improve confidence.

8.5 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 ESKD 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 rapid 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, patient who experience AKI should be followed for the resolution of AKI and to evaluate 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 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 pre-renal azotemia in the patient with CKD and AKI.
- Starch-based crystalloid solutions, phosphate-containing cathartics, and meperedine should be avoided in patients with CKD or AKI.
- Avoid subclavian lines 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 ESKD, prior episodes of AKI in the patient's medical history should be documented.

References

1. Prevention CKDST. Chronic kidney disease surveillance system. https://nccd.cdc.gov/ckd/detail.aspx?Qnum=Q677&Strat=Year.
2. 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.
3. CKD-MBD Work Group. Kidney disease: improving global outcomes (KDIGO). KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
4. 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.
5. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I, et al. World incidence of AKI: a meta-analysis. Clin J Am Soc Nephrol. 2013;8(9):1482–93.
6. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–23.
7. Hsu CY, McCulloch CE, Fan D, Ordo JD, et al. Community-based incidence of acute renal failure. Kidney Int. 2007;72(2):208–12.
8. 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.
9. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med. 2007;35(8):1837–43; quiz 52.
10. Organization WH. Ageing and health 2021. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health.
11. Kashani K, Shao M, Li G, Williams AW, Rule AD, Kremers WK, et al. No increase in the incidence of acute kidney injury in a population-based annual temporal trends epidemiology study. Kidney Int. 2017;92(3):721–8.
12. 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.
13. 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.
14. 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.
15. Nishimoto M, Murashima M, Kokubu M, Matsui M, Eriguchi M, Samejima KI, et al. Pre-operative proteinuria and post-operative acute kidney injury in noncardiac surgery: the NARA-acute kidney injury cohort study. Nephrol Dial Transplant. 2020;35(12):2111–6.
16. Wahl TS, Graham LA, Morris MS, Richman JS, Hollis RH, Jones CE, et al. Association between preoperative proteinuria and postoperative acute kidney injury and readmission. JAMA Surg. 2018;153(9):e182009.

17. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int. 2012;82(5):516–24.
18. 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.
19. 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.
20. 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.
21. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int. 2012;81(5):477–85.
22. Ikizler TA, Parikh CR, Himmelfarb J, Chinchilli VM, Liu KD, Coca SG, et al. A prospective cohort study of acute kidney injury and kidney outcomes, cardiovascular events, and death. Kidney Int. 2021;99(2):456–65.
23. 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.
24. Coca SG, King JT Jr, 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.
25. Heung M, Steffick DE, Zivin K, Gillespie BW, Banerjee T, Hsu CY, et al. Acute kidney injury recovery pattern and subsequent risk of CKD: an analysis of veterans health administration data. Am J Kidney Dis. 2016;67(5):742–52.
26. Palomba H, Castro I, Yu L, Burdmann EA. The duration of acute kidney injury after cardiac surgery increases the risk of long-term chronic kidney disease. J Nephrol. 2017;30(4):567–72.
27. James MT, Pannu N, Hemmelgarn BR, Austin PC, Tan Z, McArthur E, et al. Derivation and external validation of prediction models for advanced chronic kidney Disease following acute kidney injury. JAMA. 2017;318(18):1787–97.
28. 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.
29. Hsu CY, Chinchilli VM, Coca S, Devarajan P, Ghahramani N, Go AS, et al. Post-acute kidney injury proteinuria and subsequent kidney disease progression: the assessment, serial evaluation, and subsequent sequelae in acute kidney injury (ASSESS-AKI) study. JAMA Intern Med. 2020;180(3):402–10.
30. 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.
31. Siew ED, Parr SK, Abdel-Kader K, Eden SK, Peterson JF, Bansal N, et al. Predictors of recurrent AKI. J Am Soc Nephrol. 2016;27(4):1190–200.
32. Liu KD, Yang J, Tan TC, Glidden DV, Zheng S, Pravoverov L, et al. Risk factors for recurrent acute kidney injury in a large population-based cohort. Am J Kidney Dis. 2019;73(2):163–73.
33. Husain-Syed F, Ferrari F, Sharma A, Danesi TH, Bezerra P, Lopez-Giacoman S, et al. Preoperative renal functional reserve predicts risk of acute kidney injury after cardiac operation. Ann Thorac Surg. 2018;105(4):1094–101.
34. Sato Y, Takahashi M, Yanagita M. Pathophysiology of AKI to CKD progression. Semin Nephrol. 2020;40(2):206–15.
35. Zuk A, Bonventre JV. Acute kidney injury. Annu Rev Med. 2016;67:293–307.
36. Basile DP, Bonventre JV, Mehta R, Nangaku M, Unwin R, Rosner MH, et al. Progression after AKI: understanding maladaptive repair processes to predict and identify therapeutic treatments. J Am Soc Nephrol. 2016;27(3):687–97.
37. Whiting P, Morden A, Tomlinson LA, Caskey F, Blakeman T, Tomson C, et al. What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis. BMJ Open. 2017;7(4):e012674.
38. Doerfler RM, Diamantidis CJ, Wagner LA, Scism BM, Vaughn-Cooke M, Fink WJ, et al. Usability testing of a sick-day protocol in CKD. Clin J Am Soc Nephrol. 2019;14(4):583–5.
39. 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.
40. Manohar S, Kompotiatis P, Thongprayoon C, Cheungpasitporn W, Herrmann J, Herrmann SM. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis. Nephrol Dial Transplant. 2019;34(1):108–17.
41. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int. 2016;90(3):638–47.
42. Kwitkowski VE, Prowell TM, Ibrahim A, Farrell AT, Justice R, Mitchell SS, et al. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. Oncologist. 2010;15(4):428–35.
43. Marcolino MS, Boersma E, Clementino NCD, Macedo AV, Marx-Neto AD, Silva M, et al. Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients. Ann Oncol. 2011;22(9):2073–9.

44. Delsante M, Monroy-Trujillo JM, Carter-Monroe N, Ball DW, Rosenberg AZ. Lenvatinib-related renal microangiopathy: a case series. Virchows Arch. 2022;480(2):467–73.
45. Hilburg R, Geara AS, Qiu MK, Palmer MB, Chiang EY, Burger RA, et al. Bevacizumab-associated thrombotic microangiopathy treated with eculizumab: a case series and systematic review of the literature. Clin Nephrol. 2021;96(1):51–9.
46. Gupta S, Short SAP, Sise ME, Prosek JM, Madhavan SM, Soler MJ, et al. Acute kidney injury in patients treated with immune checkpoint inhibitors. J Immunother Cancer. 2021;9(10):e003467.
47. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. Am J Kidney Dis. 2016;68(2):287–91.
48. Kitchlu A, Fingrut W, Avila-Casado C, Chan CT, Crump M, Hogg D, et al. Nephrotic syndrome with cancer immunotherapies: a report of 2 cases. Am J Kidney Dis. 2017;70(4):581–5.
49. Daanen RA, Maas RJH, Koornstra RHT, Steenbergen EJ, van Herpen CML, Willemsen A. Nivolumab-associated nephrotic syndrome in a patient with renal cell carcinoma: a case report. J Immunother. 2017;40(9):345–8.
50. Lin JS, Wang DY, Mamlouk O, Glass WF, Abdelrahim M, Yee C, et al. Immune checkpoint inhibitor associated reactivation of primary membranous nephropathy responsive to rituximab. J Immunother Cancer. 2020;8(2):e001287.
51. Hanna RM, Lopez E, Wilson J, Barathan S, Cohen AH. Minimal change disease onset observed after bevacizumab administration. Clin Kidney J. 2016;9(2):239–44.
52. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. Balanced crystalloids versus saline in critically ill adults. N Engl J Med. 2018;378(9):829–39.
53. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(2):122–33.
54. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA. 2016;315(20):2190–9.
55. Investigators S-A, Canadian critical care trials G, Australian, New Zealand Intensive Care Society clinical trials G, United Kingdom critical care research G, Canadian nephrology trials N, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med. 2020;383(3):240–51.
56. Kalantari K, Swaminathan S. Use of gadolinium in individuals with reduced kidney function. Clin J Am Soc Nephrol. 2021;16(2):304–6.
57. Siew ED, Parr SK, Wild MG, Levea SL, Mehta KG, Umeukeje EM, et al. Kidney disease awareness and knowledge among survivors of Acute kidney injury. Am J Nephrol. 2019;49(6):449–59.
58. Hsu CY, Chinchilli VM, Coca S, Devarajan P, Ghahramani N, Go AS, et al. Post-acute kidney injury proteinuria and subsequent kidney disease progression: the assessment, serial evaluation, and subsequent sequelae in acute kidney injury (ASSESS-AKI) study. JAMA Intern Med. 2020;180:402.
59. Hung AM, Siew ED, Wilson OD, Perkins AM, Greevy RA Jr, Horner J, et al. Risk of hypoglycemia following hospital discharge in patients with diabetes and acute kidney injury. Diabetes Care. 2018;41(3):503–12.
60. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, et al. AKI and long-term risk for cardiovascular events and mortality. J Am Soc Nephrol. 2017;28(1):377–87.
61. American Society of Nephrology Renal Research Report. J Am Soc Nephrol 2005;16(7):1886–1903.
62. Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R, et al. Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. JAMA Netw Open. 2020;3(10):e2019209.