CHAPTER 28

Epidemiology, Diagnosis, and Therapy of Acute Kidney Injury

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EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is a complex syndrome associated with several etiologic factors. AKI occurs in a variety of settings with clinical manifestations ranging from a minimal elevation in serum creatinine (SCr) to anuric kidney failure.[1–3] The incidence of AKI with and without need for dialysis has been progressively increasing in the last 15 years[4] (Fig. 28.1) and is more pronounced in older hospitalized patients. Data from the USRDS shows that 1.6% of patients age 66 and older who were continuously enrolled in Medicare inpatient/outpatient had the diagnosis of AKI[4,5] (Fig. 28.2). The increasing incidence can also be explained by the growing awareness by the medical community about AKI as a main risk factor for mortality and an important contributor for chronic kidney disease (CKD).

The reported incidence of AKI is widely variable in different regions of the world (Table 28.1). In the developed world AKI is seldom a community-acquired disease; the condition develops primarily in hospitalized patients. In these regions the incidence of hospital-acquired AKI exceeds that of community-acquired AKI by 5 to 10 times, having an estimated yearly incidence of 0.15% to 7.2%.[6] In the developed world more than 20% of AKI cases occur in the intensive care unit (ICU) setting. On the other hand, in the developing world a number of cases of AKI are found in rural areas. The demographics, etiologies, and outcomes of AKI in rural settings differ from those in more developed areas. In rural regions AKI is caused predominately by snake, spider, caterpillar, or bee envenomations, or by specific infections such as leptospirosis, tetanus, or severe malaria. Those patients are managed by primary caregivers who have limited resources.

The age of AKI patients is another difference between developed and developing countries. Elderly patients predominate in the developed world whereas in the developing world AKI is generally a disease of the young. Children are more often affected in developing countries, constituting more than 15% of patients in some studies. Age differences might partially account for differences in reported survival rates between the developed and developing countries. Paradoxically, patients in developing countries might have a better chance of survival. Here younger patients develop AKI as a result of a single disease (e.g., leptospirosis or malaria) rather than from multiple organ failure, but are more prone to complications secondary to poor nutrition and resource availability (Table 28.1).

The first step for the nephrology community to better understand and quantify the clinical importance of AKI was to develop a uniform definition. Before 2004 acute renal failure (ARF) had no accepted definition resulting in more than 30 different definitions reported in the literature.[7] Consequently, epidemiologic studies used different clinical and physiologic endpoints making it difficult to compare the results between studies (Table 28.1). This lack of a uniform definition yielded discrepancies in AKI incidence, prevalence, and outcomes in various clinical settings. The reported incidence ranged from 1% to 31% and mortality from 28% to 82%.[8–10] The formation of the Acute Dialysis Quality Initiative (ADQI) group in 2000 was the beginning of a process to establish consensus and evidence based guidelines in ARF. In 2004, ADQI formulated the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification for ARF.[7] The RIFLE classification system provides three grades of severity for AKI based on the maximal increase in SCr or decrease in urine output from the baseline condition: injury—risk (class R), injury (class I), and failure (class F)—and two outcome classes (loss and end-stage renal disease [ESRD]) (Table 28.2).

The clinical predictive ability of the RIFLE classification has been extensively validated in large general and ICU populations.[8,11–15] In a single center retrospective cohort study, including 5,383 patients admitted during a 1-year period, the incidence of AKI was 67.2%. In that cohort AKI was associated with an increased risk for hospital mortality compared to those who never developed AKI. The higher incidence that might have been considered unusual before the RIFLE era was confirmed in other studies that applied the criteria.[8,11–15]

The ADQI group, associated with representatives of nephrology societies (ASN, ISN, and NKF) and the European

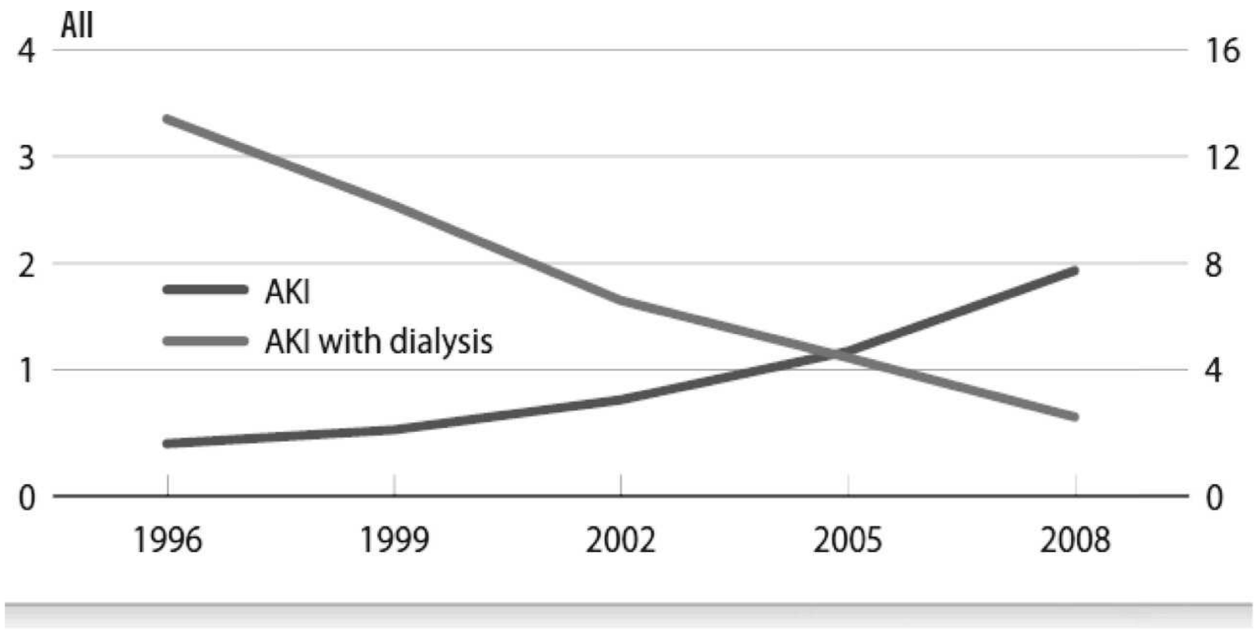


FIGURE 28.1 Hospitalizations for acute kidney injury, with or without dialysis. (Modified from Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis.* 2010;55(1 Suppl 1):S1–420, A426–427.)

Society of Intensive Care Medicine, created the Acute Kidney Injury Network (AKIN) as an independent collaborative network intended to facilitate international, interdisciplinary, and intersocietal collaborations.[16] One of the tasks proposed by the AKIN was to further refine the AKI definition. In 2007, a modified version of the RIFLE classification was published, also known as the AKIN classification (Table 28.2).[17] The terms Risk, Injury, and Failure were replaced by stages 1, 2, and 3, respectively. An absolute increase in creatinine of at least 0.3 mg per dL was added to stage 1. Patients starting renal replacement therapy (RRT) are automatically classified as stage 3, regardless of their SCr or urine output. The outcome categories Loss and ESRD were eliminated. Another difference between RIFLE and the AKIN classification is the 48-hour time frame within which the diagnosis of AKI is made, "AKIN criteria . . . change in creatinine should occur within 48h."[17] However, after the diagnosis is established, staging should be applied with no time frame constraint. Additionally, the glomerular filtration rate (GFR) criteria were eliminated.

In the RIFLE and AKIN classification systems patients are classified based on the worst category achieved. This is intended to describe the change or trend in AKI severity over time. Several studies in the ICU population have validated the concept verified in clinical practice that patient outcome progressively worsens with the maximal severity of AKI achieved.[8,12,14,18–20] Over 71,000 patients were included in published studies with the RIFLE classification system; these studies showed a stepwise increase in relative risk (RR) for death going from Risk (RR: 2.40) to Injury (RR: 4.15) to Failure (6.37).[21] Osterman and Chang[22] performed a retrospective analysis of a database of 41,972 patients admitted to ICU. AKI based on RIFLE occurred in 35.8% of patients: 17.2% Risk, 11% Injury, and 7.6% Failure. Patients with Risk, Injury, and Failure had a hospital mortality of 20.9%, 45.6%, and 56.8%, respectively, compared to 8.4% among non-AKI patients. Abosaif et al.[23] retrospectively applied the RIFLE classification in order to evaluate its sensitivity and specificity to predict renal and patient outcomes in 183 critically ill patients with AKI. Mortality rate in the ICU (60 days, 74.4%) and 6-month mortality rate (86%) were significantly greater in the RIFLE-Failure group compared with all groups. Cruz et al.[15] conducted a prospective multicenter study in 19 ICUs in northeastern Italy. Of 2,164 ICU patients who were admitted during the study period, 234 (10.8%) developed AKI whereas 3.3% were treated with RRT. Of the AKI patients, 19% were classified as Risk, 35% as Injury, and 46% as Failure. Overall, ICU mortality was higher among those in RIFLE class Failure (49.5% vs. 20% in R, 29.3% in I).

Hoste and colleagues[14] performed a retrospective single-center study on 5,383 patients admitted during a 1-year period in seven ICUs. AKI occurred in 67% of ICU admissions, and 12% reached a maximum RIFLE class of Risk, 27% Injury, and 28% Failure. Interestingly, among the patients that reached a level of Risk, 56% progressed to either Injury or Failure. Patients with maximum RIFLE class Risk, Injury, and Failure had hospital mortality rates of 8.8%, 11.4%, and

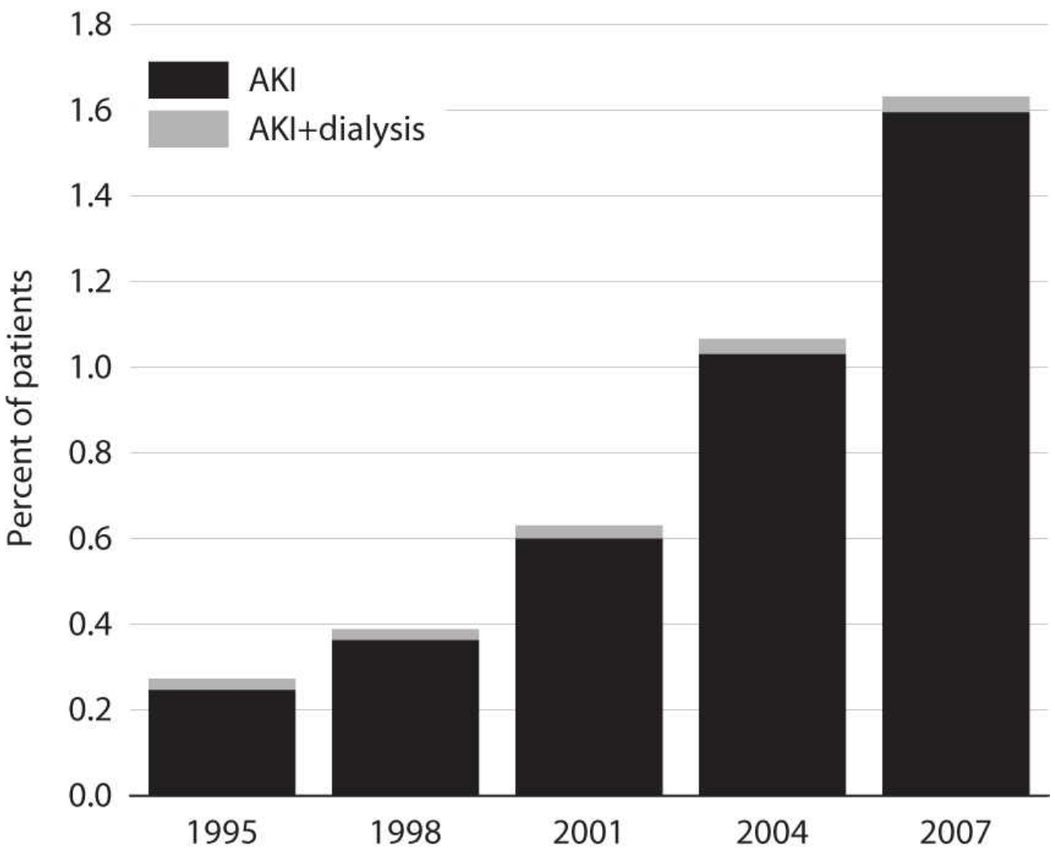


FIGURE 28.2 General Medicare patients age 66 and older continuously enrolled in Medicare inpatient/outpatient, surviving and without end-stage renal disease. (From Collins AJ, Foley RN, Herzog C, et al. United States Renal Data System 2008 Annual Data Report. *Am J Kidney Dis.* 2009;53(1 Suppl):S1–374.)

28.1 Epidemiologic Population Studies of Acute Renal Failure

Country	Definitions of ARF	Incidence (pmp)	Reference
USA	Increase in serum creatinine of 0.5 mg/dL (44.2 mol/L) in patients with baseline serum creatinine <1.9 mg/dL (168.0 mol/L) Increase in serum creatinine >1.0 mg/dL (88.4 mol/L) in patients with baseline serum creatinine 2.0–4.9 mg/dL (176.9– 433.2 mol/L) Increase in serum creatinine of 1.5 mg/dL (132.6 mol/L) in patients with baseline serum creatinine >5 mg/dL (442.0 mol/L)	1% of all hospital admissions All ARF was acquired out of hospital	251
Kuwait	Unknown	95	252
England	Serum creatinine >500 mol/L (5.7 mg/dL) Need for RRT	175 22	253
France	Unknown	104	254
Spain	Sudden increase of serum creatinine >177.0 mol/L (2.0 mg/dL) or sudden increase in serum creatinine >50% when prior renal function was normal or mild CKD was present Need for RRT	209[a] 57	255
Scotland	Serum creatinine 300 mol/L (3.4 mg/dL) Serum creatinine 500 mol/L (5.7 mg/dL) Need for RRT	620 102 50	256
USA (African Americans)	Serum creatinine 2 mg/dL (176.8 mol/L) without renal disease	5/1,000[b] hospital admissions	257
Australia	Need for RRT and mostly critically ill	135	258
England	Serum creatinine 300 mol/L (3.4 mg/dL)	486	259
Scotland	Need for RRT	203	260
South India	Unknown	336	261
Brazil	Increase in serum creatinine of at least 0.5 mg/dL (44.2 mol/L), admission serum creatinine >1.4 mg/dL (123.8 mol/L) for men or >1.3 mg/dL (114.9 mol/L) for women, and a normal serum creatinine level at admission, but presenting an increase during hospitalization	325/3,684 renal evaluations[c]	262
England	Serum creatinine 500 mol/L (5.7 mg/dL) or need for RRT Multiorgan ARF Single-organ ARF	380 125	263

[a]50% of ARF occurred before admission to hospital, 50% developed in hospital.
[b]Represents 79% of all ARF cases per year in one hospital.
[c]53% community-acquired ARF, 47% hospital-acquired ARF.
ARF, acute renal failure; CKD, chronic kidney disease; pmp, per million people; RRT, renal replacement therapy.
From Lameire N, Van Biesen W, Vanholder R. The changing epidemiology of acute renal failure. Nat Clin Pract Nephrol. 2006;2(7):364–377.

28.2 RIFLE and AKIN Classification Systems

Stage	RIFLE	Serum Creatinine Criteria	Urine Output Criteria
1	R	Increase to ≥150%–200% from baseline (AKIN and RIFLE)[a] or increase in serum creatinine >0.3 mg/dL (AKIN)	Less than 0.5 mL/kg/h for more than 6 h
2	I	Increase in serum creatinine >200%–300% from reference	Less than 0.5 mL/kg/h for more than 12 h
3	F	Increase in serum creatinine >300% from reference	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h

[a]Within 48 hours for AKIN criteria, within 7 days for RIFLE criteria.

26.3%, respectively, in contrast to 5.5% in non-AKI patients. RIFLE classes were still associated with hospital mortality after adjusting for multiple covariates (baseline severity of illness, case mix, race, gender, and age). These findings showed that patients with RIFLE-Risk are indeed at significant risk of progression to more severe AKI. Patients with RIFLE class Injury or Failure incur a significantly increased length of stay and an increased risk of in-hospital mortality compared with those who do not progress past Risk or those who never develop AKI.

The increasing severity of illness in critically ill patients with AKI is one of the contributors to the persistently high mortality rate associated with this syndrome. Observational studies suggest that critically ill patients with AKI are increasingly older, have more comorbid diseases, have a higher incidence of septic, and have greater severity of illness and organ failure scores. Two severity of illness scoring systems are widely used: the Acute Physiology and Chronic Health Evaluation (APACHE) score and the Sequential Organ Failure Assessment (SOFA) score.[24,25] Although patients developing AKI have shown a significant decrease in mortality rate in the last decade,[25–27] the persistently high mortality in patients with multiorgan system failure remains a challenge. This emphasizes the need for early assessment and intervention in all cases of AKI. It is apparent that AKI is associated with substantial morbidity, mortality, and cost.

The financial costs of AKI are high. Fischer et al.[28] performed a multicenter analysis in 23 Massachusetts hospitals for a 2-year period (1999 to 2000). They identified 2,252 records of patients hospitalized with uncomplicated ARF. Patients hospitalized with uncomplicated ARF incurred median direct hospital costs of $2,600, median hospital length of stay (LOS) of 5 days, and mortality of 8%. Dialysis was independently associated with significantly greater hospital costs and LOS for patients with uncomplicated ARF ($P < 0.05$) compared to patients with other commom medical diagnoses.[28]

The cost of RRT for patients with AKI is high; however, information on the costs of the three dialytic techniques for AKI is minimal. In a Canadian ICU, the cost of dialysis was $3,486 to $5,117 (Canadian) per week for continuous renal replacement therapy (CRRT).[29] For intermittent hemodialysis (IHD), major costs include the need for supervision by a trained dialysis nurse, which can become an economic issue if IHD is performed on a frequent or daily basis. For CRRT, major costs include disposables and replacement fluids. Most investigators have found that CRRT costs are somewhat greater than IHD.[30,31] An evaluation of total hospital costs[32] showed that from the start of RRT to hospital discharge patients on CRRT total cost was US$57,000 more than that for those on IHD. A recent cost analysis of the of RRT for patients with AKI estimated that mean adjusted total costs were U$1,342/week for IHD compared to U$3,486/week for CRRT[30] and no difference was found in the outcome, renal recovery at hospital discharge. However, there was a nonsignificant statistical trend toward enhanced renal recovery in the CRRT group despite a significantly lower mean arterial pressure and a trend toward higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Considering that nonrecovery of renal function would adversely affect quality of life, a modality that enhanced the rate of renal recovery would offer an important advantage, even if there were no difference in survival across modalities.

Parameters for Acute Kidney Injury Diagnosis

Serum Creatinine

Therapeutic interventions are generally based on an evaluation of clinical data and diagnostic information. In AKI the importance of timing of diagnosis was poorly appreciated as therapeutic interventions have generally been lacking, and the small number of studies reported have failed to improve

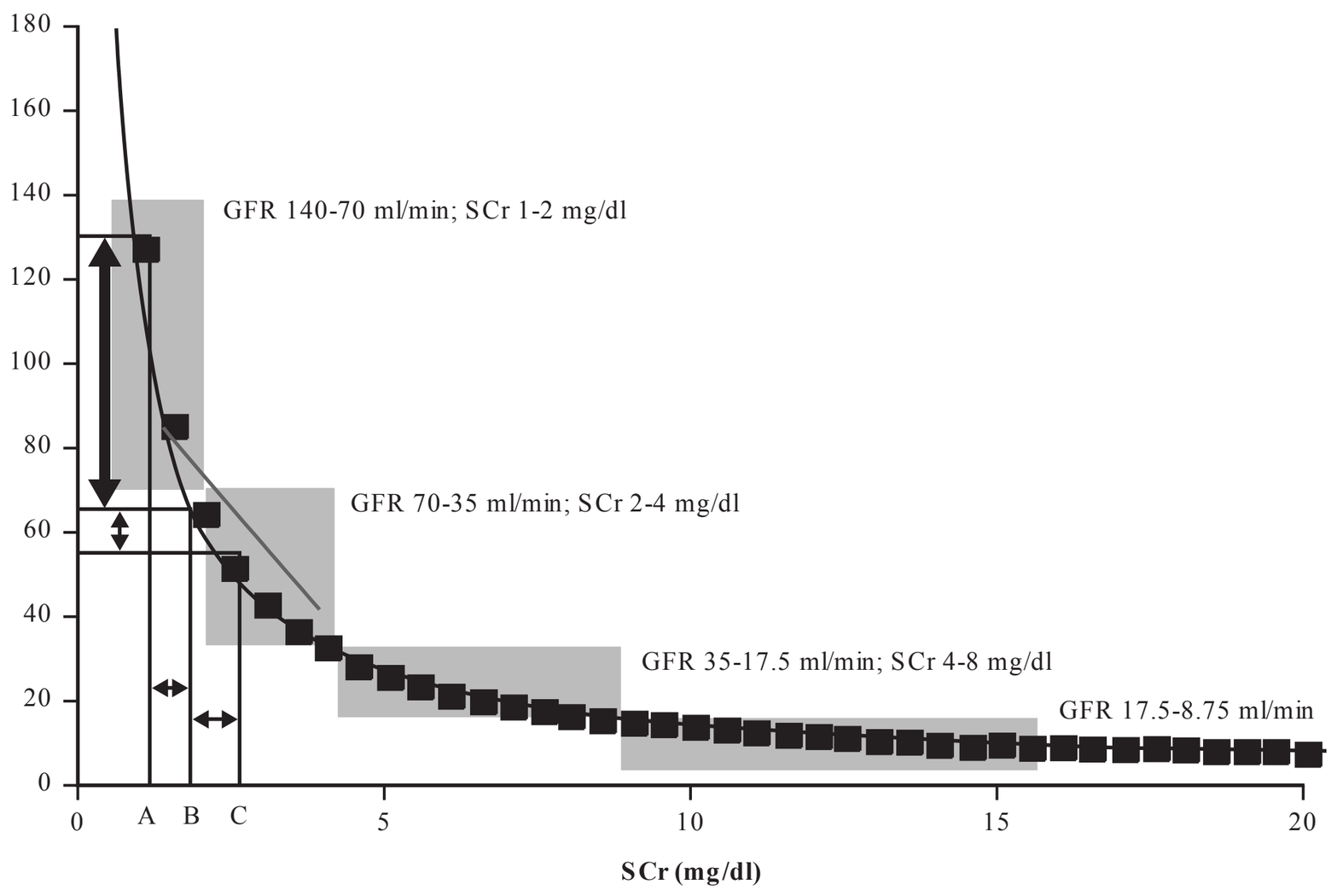
outcomes. In the last decade, the concept of interventions based on "windows of opportunity" coupled with targeted therapy became evident in other ischemic events such as acute chest pain syndromes and stroke. The importance of finding early diagnostic information in AKI has since been highlighted and the development of technology has facilitated the search for new biomarkers of kidney injury.

The current criteria for AKI diagnosis and classification, RIFLE and AKIN, are still based on SCr incremental concentrations and decreased urine output. Many characteristics other than renal function, such as age, muscle mass, catabolic rate, and race, influence SCr concentrations. In addition, SCr levels depend not only on renal elimination but also on creatinine generation and volume of distribution.[33] Given the exponential relation of SCr and GFR, significant decreases in GFR are reflected as small increases in SCr in the early phases of injury (Fig. 28.3).

In a steady state setting a reasonable approximation is that each time the GFR halves, the SCr concentration doubles. Thus, steady state GFRs of 100, 50, 25, 12.5, and 6.25 mL per minute are associated with increasing SCr concentrations ranging from 1 to 16 mg per dL; however, there is wide range depending on the level of extrarenal clearance that is accentuated as kidney function declines and may contribute to up to 40% of total clearance. AKI often occurs in a nonsteady state in which the three determinants of SCr concentration (production, volume of distribution, and renal elimination) fluctuate.[33] Computerized models derived from AKI patients demonstrate that several patterns of change in GFR occur during development and recovery from AKI. These GFR changes are poorly reflected by daily changes in SCr concentration.[33] Moreover, the rise in SCr that occurs in AKI is a post facto finding. In critically ill patients, a nonsteady state condition and the positive cumulative fluid balance enhances the insensitivity of SCr as a parameter of renal dysfunction.[34] Hoste et al. showed that in a group of recently admitted ICU patients with normal SCr the 1-hour urinary creatinine clearance revealed values lower than 80 mL/min/1.73 m^2 in 46.2% of the patients.[35] These data suggest that SCr is not a reliable tool to detect even moderate kidney dysfunction in AKI patients.

Blood Urea Nitrogen

Blood urea nitrogen (BUN) is also used as a parameter to evaluate renal function. However, elevations in BUN level are often, but not always, due to a decrease in GFR. Some factors enhance urea production, such as gastrointestinal bleeding, corticosteroid therapy, and high-protein diet. In conditions of decreased intravascular effective volume like decompensated heart failure, increases in BUN are not proportional to the rise in SCr level and fall in GFR. The usual BUN:SCr ratio is about 10:1 and the BUN and SCr increase by 10 to 15 and 1.0 to 1.5 mg/dL/day, respectively, in the absence of GFR. Increases in the basal metabolic rate that occur with fever or glucocorticoid administration enhance these daily rates. Although an increase in the BUN/



GFR, glomerular filtration rate; SCr, serum creatinine

FIGURE 28.3 Relationship between serum creatinine and glomerular filtration rate (GFR). Changes in serum creatinine represent smaller changes in GFR as renal functions decreases. Creatinine increase from A to B corresponds to a GFR decrease of GFR of 130 to 70 mL per minute, whereas from B to C the same delta creatinine corresponds to a decrease in GFR from 70 to 50 mL per minute. (Modified from Finn WF. The clinical and renal consequences of contrast-induced nephropathy. *Nephrol Dial Transplant*. 2006, 21(6):i2-i10.)

creatinine ratio has been used for many years to help to differentiate between prerenal and renal azotemia, BUN can increase independently from SCr in situations characterized by decreased glomerular perfusion pressure such as heart failure. Some studies have already shown elevations in BUN independently from SCr levels and demonstrated that these two parameters are not only a reflection of the severity of renal dysfunction, but rather the consequence of two distinct pathologic processes.[36–38] The activation of renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system is responsible for decreasing the glomerular perfusion pressure and GFR. The increment in vasopressin levels upregulates aquaporin-2 and urea transporter expressions and increases water and urea reabsorption. Urea, in contrast to SCr, is not secreted but reabsorbed by the renal tubules. The increased reabsorption of sodium and water, rather than the reduced GFR, enhances reabsorption of urea and increases BUN levels. Thus, BUN levels and BUN/creatinine ratio could be a more effective way to assess circulatory volume than GFR, which is regulated by the pressure difference between glomerular afferent and efferent arterioles.[39] In heart failure and possibly in other settings where underfilling is part of the physiopathologic process, the rise in BUN greater than any fall in GFR is a marker of the neurohumoral axis activation.[40]

In selected circumstances, it may not be clear if an elevated BUN:SCr ratio is due to an acute or chronic process. In this circumstance review of previous records is helpful.

Oliguria

Although the hydration status, osmolar excretion, as well as a large dose of diuretics will influence urine volume, and severe AKI can occur with normal urine output, the urinary flow rate also may provide helpful information about the cause of AKI. Sustained periods of anuria suggest urinary tract obstruction as the cause of AKI. Other rare causes of anuria include rapidly progressive glomerulonephritis, mechanical occlusion of renal blood flow, and diffuse renal cortical necrosis. Nonoliguric varieties of AKI are common, ranging from 25% to 80% of all cases of AKI with 33% nonoliguric at AKI diagnosis.[41–43] The nonoliguric state may be present in all types of AKI including those following surgery, trauma, hypotension, nephrotoxins, and rhabdomyolysis. Several factors may contribute to the devlopment of nonoliguric AKI: use of volume expansion, high-dose potent diuretic agents, high osmolar loads, and renal vasodilators. Another contributory factor is aggressive fluid resuscitation and improved supportive management of critically ill patients. However, nonoliguria may mask the underlying severity of AKI and lead to delayed recognition.

The definition of oliguria changed after the RIFLE and AKIN classification system. The AKIN group proposed the hourly measurement of urine volume, providing an opportunity to treat urine flow as a continuous rather than as an interval physiologic variable, with more time points for the diagnosis of oliguria and detection of AKI. Although fluctuations in this parameter can result from external influences, such as drug administration, the pattern of change can be detected earlier with more frequent observations. Experimental studies conducted in laboratory models of AKI, as well as clinical studies, have clarified the pathophysiologic aspects underlying the variations of urine flow rate in AKI.[44,45] In a study of 25 patients with predominantly renal ischemia-associated AKI, Rahman and Conger found that the urine flow rate strongly correlated with residual GFR.[45] In that study urine flow rate did not correlate with selected aspects of renal tubular function such as urine:SCr or the fractional excretion of sodium.

However, because of the difficulties in measuring and recording the hourly urine output, the AKIN oliguria criterion was evaluated in fewer studies than the SCr criterion. Of the studies evaluating the urine output criterion most were retrospective and used a modified definition of evaluating urine volume in 2 to 12 or 24 hours and shortening the time of observation to the first 24 hours of ICU admission or postoperative period. In a retrospective study Barrantes et al.[46] evaluated the outcomes of hospitalized patients classified by the AKIN criteria, using both the urine output (UO) and SCr criteria in the first 48 hours after ICU admission. Comparing patients that developed AKI using the UO, SCr, or both criteria, they found that UO criterion did not affect the AKI associated mortality. Joannidis et al.,[47] using the SAPS 3 database of ICU patients, assessed 24-hour urine volume for 48 hours. Patients with AKI defined by the lowest urine volume had higher mortality compared to non-AKI patients. In a prospective cohort of cardiac surgery patients, Haase et al.[48] subclassified the AKI patients based exclusively in the UO criterion (over a 48-hour period). Only those patients that reached a RIFLE-F or AKIN stage 3 had significantly longer ICU and hospital lengths of stay and a higher mortality rate (compared to non-AKI patients and those with maximum RIFLE-R/I and AKIN stage 1/2). In a systematic review,[21] the relative risk for death among studies that used both SCr and UO criteria was lower than in those using only the SCr criterion. Hoste and Kellum,[19] in a review including 10 studies, showed that patients in the RIFLE Risk class defined by the SCr criterion were more severely ill than those in the same class defined only by the UO criterion. Hoste et al.[14] also observed that patients in Failure based on the RIFLE GFR criterion had a slightly higher mortality than those in Failure based on the UO criterion. In a study by Cruz et al., RIFLE classes (using creatinine and UO criteria together) were the strongest predictor of ICU mortality in multivariable analysis.[15] In that study, the analysis was based only on the SCr criterion; the RIFLE class was sustained as an independent predictor of ICU mortality but with inferior statistical power. Based only on the UO criterion, RIFLE class did not emerge as an independent predictor.

These clinical observations, and a large body of experimental data, suggest the residual level of GFR is the primary determinant of urine flow in patients with AKI. The higher level of residual GFR in nonoliguric patients is

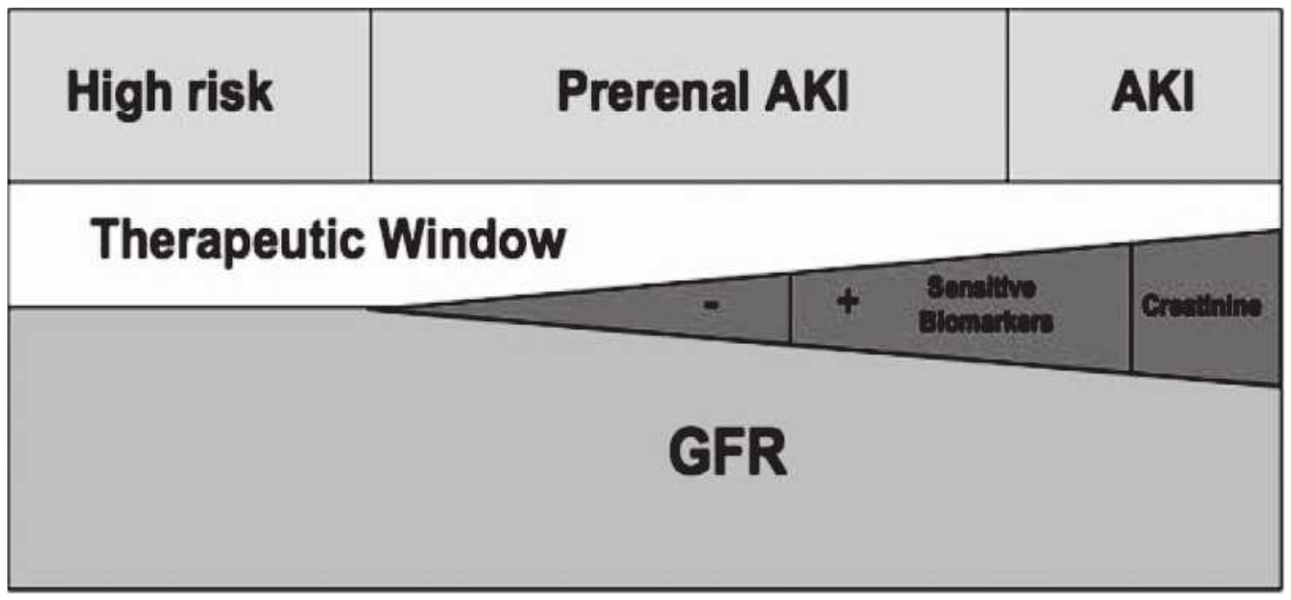


FIGURE 28.4 Time frame association for assessment of risk and early detection of acute kidney injury. Time runs along the *x*-axis, and the figure depicts a closing "therapeutic window" as injury evolves and kidney function worsens. Biomarkers of injury and function will begin to manifest as the condition worsens, but traditional markers of function (e.g., urea nitrogen and creatinine) will lag behind hypothetical "sensitive" markers of kidney injury. Mortality increases as kidney function declines. (From Himmelfarb J, Joannidis M, Molitoris B, et al. Evaluation and initial management of acute kidney injury. *Clin J Am Soc Nephrol.* 2008;3(4):962–967.)

compatible with improved survival and lower morbidity in these patients. However, one needs to be aware that there is a distinction between spontaneous nonoliguria from diuretic induced urine flow with respect to underlying GFR and nonoliguria does not automatically imply a higher GFR.

Biomarkers

The importance of early detection of AKI has been emphasized as an earlier diagnosis would provide a wider window to perform supportive and therapeutic interventions (Fig. 28.4). The recognition of the insensitivity to detect AKI by the most commonly used surrogates of kidney function (SCr and UO) has led to extensive efforts to identify alternative biomarkers for AKI diagnosis, including urine and serum biomarkers. Compared to the use of more sensitive biomarkers of kidney injury, SCr delays the AKI diagnosis by 48 to 72 hours.[49–52] Most of the studies have focused on the ability of these biomarkers to detect AKI earlier than the classical parameters, but biomarkers may be also useful to predict the course and prognosis of AKI (Fig. 28.5). Several promising candidates have emerged, demonstrating reasonable diagnostic performance for AKI up to 48 hours prior to a significant change in SCr.[53,54] Although the commercial platforms are becoming available for research use, the knowledge for the clinical application, utility, and diagnostic value of these early biomarkers remains to be validated. These new candidates are being tested in different AKI clinical scenarios. The different abilities to detect renal injury and estimate GFR are associated with their pathophysiology (Fig. 28.6). AKI biomarkers differ on the basis of how they

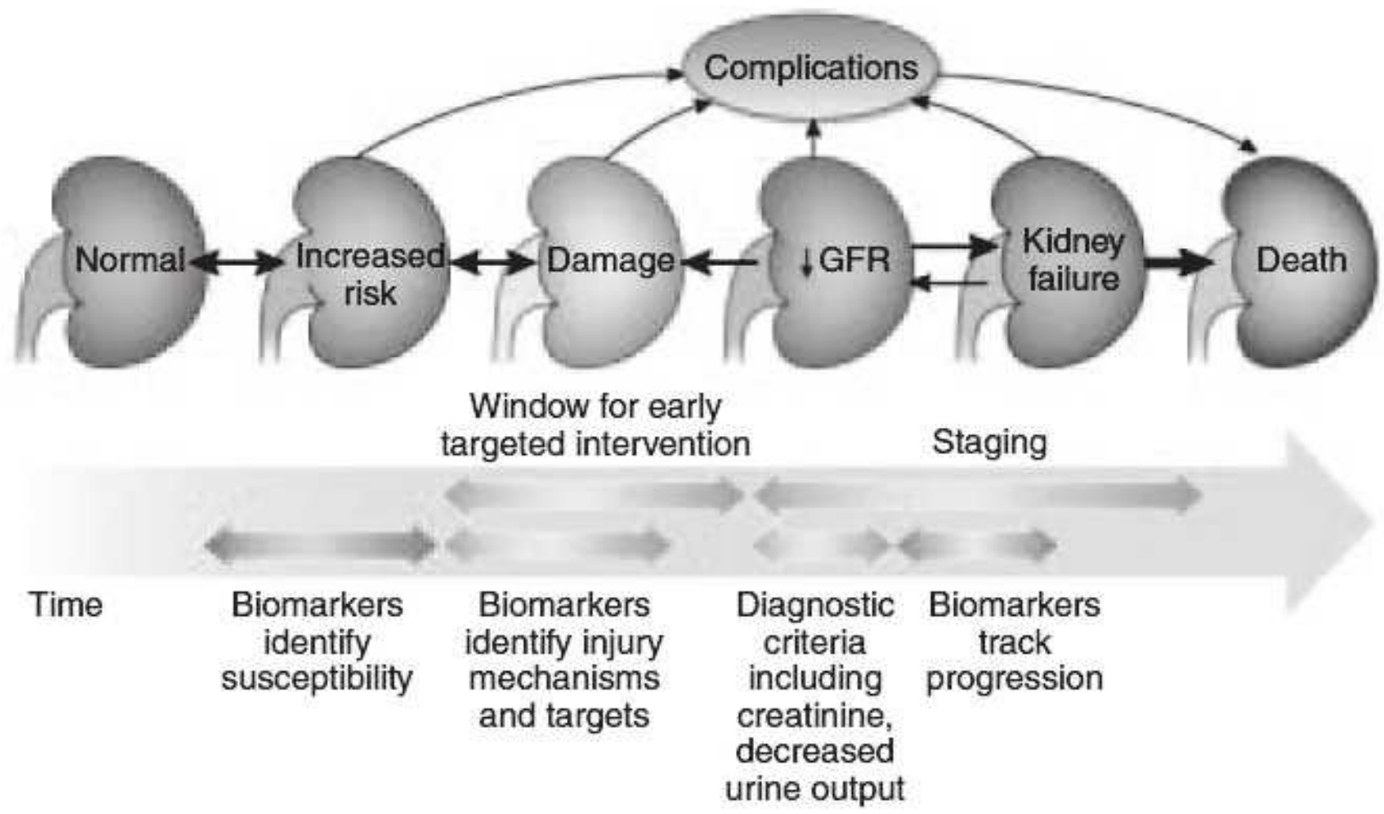


FIGURE 28.5 Conceptual framework for acute kidney injury. Surveillance could be initiated for high-risk individuals on the basis of clinical and biomarker criteria. Sequential assessment of biomarkers may permit identification of a window of opportunity in which kidney injury has been initiated but has not progressed to renal functional change. The duration of this window is inherently dependent on the type and site of injury and the nature and specificity of the biomarkers to determine the targets for intervention. Progression of kidney injury would be determined by development of functional changes staged on the basis of the severity of kidney injury. Biomarkers could further define progression, determine need for additional interventions, and predict prognosis. *GFR*, glomerular filtration rate. (Modified from Mehta RL. Timed and targeted therapy for acute kidney injury: a glimpse of the future. *Kidney Int.* 2010;77(11):947–949.)

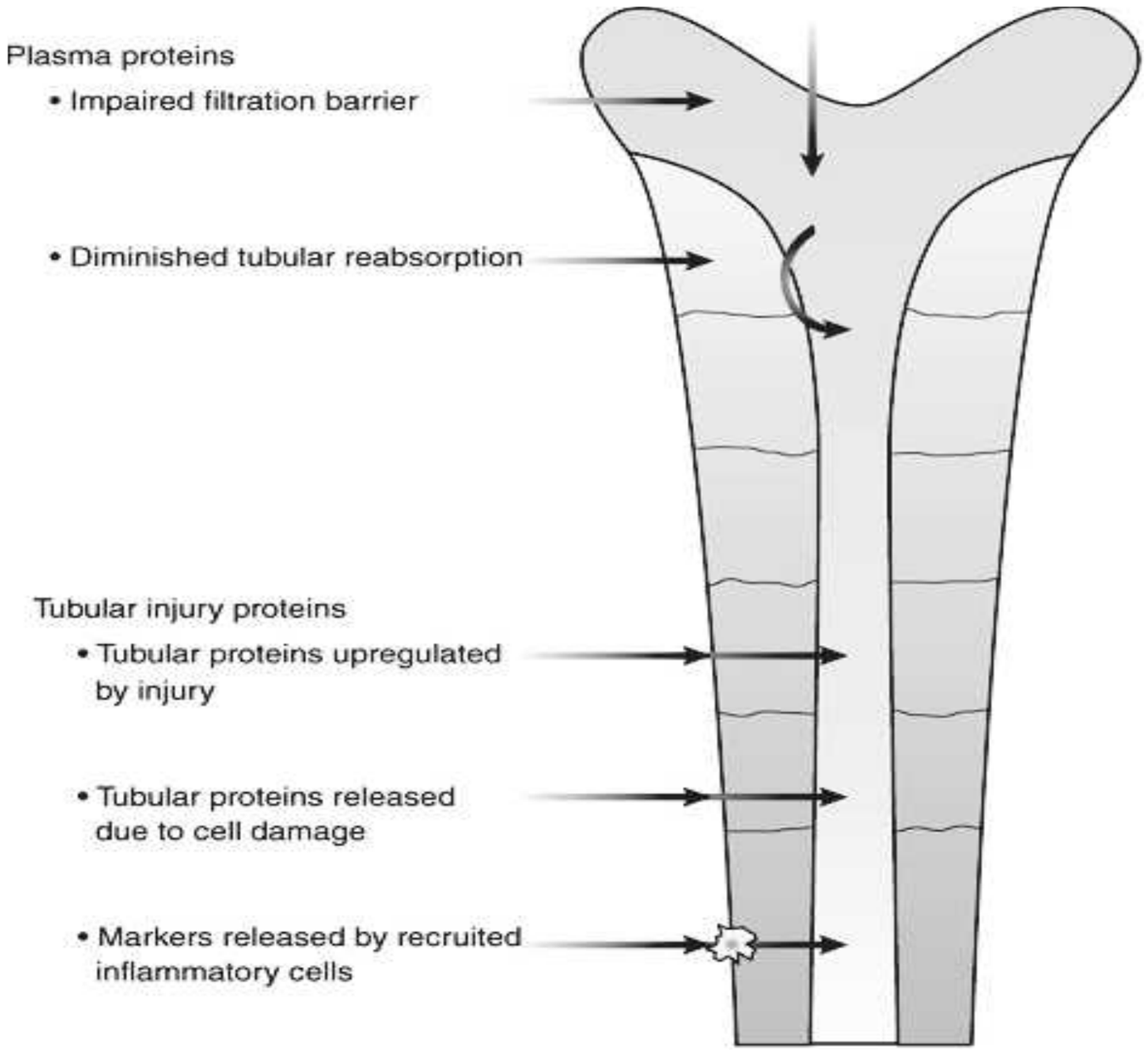


FIGURE 28.6 Pathophysiology of urinary biomarkers. Schematic representation of the mechanisms by which proteins escape into the urine. (Adapted from Briggs JP. The hunt for the perfect biomarker for acute kidney injury: back to gamma-trace? *Kidney Int.* 2008;74(8):987–989.)

enter the urine, either through filtration, upregulation, and secretion or through leakage from damage of a constitutive marker. The time sequence and magnitude of biomarker elevations are unique and may depend on the nature and severity of injury.

In addition to potentially facilitating an earlier diagnosis, these biomarkers will also allow for retesting preventive and therapeutic drugs that have failed in clinical trials that used SCr as a parameter to guide intervention. Another area of possible application for the new biomarkers is assisting in decisions to initiate RRT in patients with AKI. The main biomarkers being tested and some clinical data on their use are summarized below.

Cystatin C

Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells. Because of its low molecular weight it is freely filtered at the glomerulus and reabsorbed and catabolized, but not secreted by the renal tubule. Plasma levels correlate with GFR and, unlike creatinine, are not significantly affected by age, gender, race, or muscle mass. In human studies, both pCyC and uCyC have been shown to predict AKI, although its superiority over SCr has not been a universal finding.[55–57] Recently, Herget-Rosenthal et al.[58] compared cystatin C with creatinine for the diagnosis of AKI in a series of 85 patients. Increases in serum levels of cystatin C were detectable 1 to 2 days earlier than comparable changes in SCr. In another study measuring plasma Cr (PCr) and pCyC in 444 adults on ICU admission, of whom 124 already had AKI on entry, pCyC moderately predicted death or RRT (area under curve [AUC] 0.61, 95% confidence interval [CI], 0.53–0.68) and performed similarly as PCr (AUC 0.60, 95% CI, 0.51–0.67).[59] In a cohort of 151 AKI patients from a small multicenter study, Royakkers et al.[60] used the RIFLE classification system to define AKI and compare the performance of sCyC and uCyC as early biomarkers for AKI. Urinary CyC had no diagnostic value during the days prior to AKI diagnosis by SCr (AUC <0.50). In addtion, sCyC and uCyC determined on the first day of AKI diagnosis were poor predictors for the need for RRT (AUC $= 0.66$).[60]

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kD protein, originally characterized in and secreted by neutrophils, that is bound to gelatinase. The physiologic role of NGAL in the kidney is unknown; however, it is believed to play a role in renal morphogenesis.[61] High throughput functional genomic studies have identified NGAL as one of the most upregulated transcripts in whole kidney tissue very early after acute injury. Downstream proteonomic studies using animal models have also revealed the 25-kD NGAL protein to be one of the earliest and most robustly produced proteins in the kidney after ischemic or nephrotoxic AKI.[62] Several clinical studies have suggested that urine NGAL expression may serve as an early marker of AKI.[63–66] In a clinical trial of 71 children who underwent cardiac surgery, urinary NGAL increased within 2 hours of cardiopulmonary bypass to a level of >50 μg per L in all 20 children who had

an increase in SCr of >50% (RIFLE Risk) and in only one of the 51 children who did not meet the RIFLE definition of AKI.[67] Urinary NGAL also was evaluated in adult patients who underwent cardiac surgery, with far less impressive results.[68] In a cohort of 81 such patients at a single institution, 16 developed AKI, as defined by RIFLE. Preoperative urinary NGAL levels were comparable among patients who did and did not develop AKI and were not significantly different immediately after surgery. However, within 1 hour after surgery, the urinary NGAL concentration began dropping in patients who did not develop AKI but continued to rise in patients with AKI, peaking at 3 hours and remaining elevated for 24 hours.[68] In one study evaluating urinary NGAL levels in emergency room patients, the AUC for NGAL to detect AKI (0.948) did not significantly differ from the curve for SCr (0.921). Nevertheless, there was very little overlap in NGAL values in patients with AKI and prerenal failure, whereas SCr values overlapped significantly in AKI patients and in those that reversed the condition within 48 hours.[64] Urinary NGAL was measured in hospitalized patients with established AKI at study inclusion and after 2 days. Of the 145 patients analyzed, 75 had intrinsic AKI, 32 had prerenal AKI, and 38 patients could not be classified. Urinary NGAL levels effectively discriminated between intrinsic and prerenal AKI (AUC 0.87). An NGAL level over 104 μg per L indicated intrinsic AKI (likelihood ratio 5.97), whereas an NGAL level of 47 μg per L made intrinsic AKI unlikely (likelihood ratio 0.2). A logistic regression analysis showed that NGAL independently predicted a composite outcome (worsening RIFLE severity class within 7 days, need for RRT, and in-hospital mortality) after correcting for demographics, comorbidities, creatinine, and RIFLE class. The authors concluded urinary NGAL was useful in classifying and stratifying patients with established AKI.[69]

Several studies have examined the clinical endpoint of RRT initiation using NGAL.[70] Urine or plasma/serum NGAL have been studied in various clinical settings including children and adults (Table 28.3). In a meta-analysis of studies that evaluated NGAL accuracy for diagnosis and prognosis, 1,948 patients from nine studies were included. The overall incidence of RRT was 4.3%, and the pooled analysis yielded an AUC of 0.782 (95% CI, 0.648–0.917) for discriminating patients who would receive RRT associated with AKI. For a cut-off in NGAL of 278 ng per mL, the sensitivity was 76% and specificity was 80%.[70] However, these studies included diverse patient populations, and the specimens and assays used in obtaining this estimate varied, making it difficult to translate the results to bedside clinical use.

N-acetyl-β-D-glucosaminidase (NAG)

N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal enzyme (>130 kDa) that has been localized to lysosomes in several human cells including the renal tubules. The large molecular weight precludes glomerular filtration implying that urinary

28.3 NGAL for Prediction of Renal Replacement Therapy

Reference	Specimen	Population		RRT Endpoint	Results from Pooled Analysis
Cruz[268]	Plasma	ICU	Adults	15/301 (5%)	
Constantin[269]	Plasma	ICU	Adults	7/88 (8%)	
Wheeler[270]	Plasma	ICU	Pediatric	22/143 (15%)	
Nickolas[271]	Urine	Emergency room patients	Adults	12/541 (2%)	AUC 0.78 (95% CI, 0.65–0.92) Diagnostic odds ratio 12.9 (95% CI, 4.9–33.9) At cut-off 278 ng/mL, sensitivity 76%, specificity 80%
Koyner[272]	Plasma and urine	Cardiac surgery	Adults	7/72 (10%)	
Haase-Fielitz[273]	Serum	Cardiac surgery	Adults	4/100 (4%)	
Wagener[274]	Urine	Cardiac surgery	Adults	5/81 (6%)	
Wagener[275]	Urine	Cardiac surgery	Adults	8/426 (2%)	
Bennett[276]	Urine	Cardiac surgery	Pediatric	4/196 (2%)	

RRT, renal replacement therapy; ICU, intensive care unit; AUC, area under curve; CI, confidence interval.
Adapted from Haase M, Bellomo R, Devarajan P, et al. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54(6):1012–1024.

elevations are from tubular origin. Increased activity suggests injury to tubular cells or may reflect increased lysosomal activity. NAG catalyzes the hydrolysis of terminal glucose residues in glycoproteins and is the most active glycosidase found in proximal tubular epithelial cell lysosomes. Urinary NAG activity remains elevated during different kinds of active renal disease.[71] The diagnostic and prognostic ability of nine urinary biomarkers, including NAG, was evaluated in a cross-sectional study with 102 patients with established AKI and compared to 102 subjects without AKI.[72] The non-AKI subjects included healthy controls, ICU patients and subjects who underwent coronary angiography, whereas AKI patients were recruited at initial nephrology consultation. An age-adjusted analysis, using log-transformed biomarker values, showed NAG to be a significant predictor for RRT, mortality, and composite endpoint. The median normalized NAG level in AKI patients who underwent RRT was 0.06 U per mg Cr, versus 0.02 U per mg Cr in those who did not.

In another study including 635 patients presenting to the emergency room, urine NAG was not predictive of a composite outcome of nephrology consultation, ICU admission, RRT initiation, and mortality on multivariable analysis which included SCr and BUN.[64]

Kidney Injury Molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein with a cleavable ectodomain localized in the apical membrane of dilated tubules in acute and chronic injury. KIM-1 and its soluble ectodomain in urine (90 kDa) are believed to play a role in the regeneration processes after epithelial injury. It is undetectable in normal kidney tissue but expressed at very high levels in proximal tubule epithelial cells in human and rodent kidneys after ischemic or toxic injury.[73] A small study in six patients with confirmed acute tubular necrosis (ATN) showed KIM-1 expression via immunohistochemistry on kidney biopsy. The same investigators subsequently examined urinary KIM-1 in 40 patients and found KIM-1 levels elevated to a higher degree in patients with ischemic acute tubular necrosis (ATN) compared to patients with contrast nephropathy, other forms of AKI, CKD patients, and normal controls.[74] In a cohort of adults undergoing coronary artery bypass graft (CABG), urinary KIM-1 levels were predictive of subsequent AKI (sensitivity 0.74, specificity 0.9, AUC 0.83) at 12 hours postsurgery. Other studies also suggest that urinary KIM-1 may be useful in identifying ischemic ATN.[49,75,76]

In a study by Liangos et al., the AUC for prediction of RRT or death for KIM-1 was 0.61 (95% CI, 0.53–0.61), comparable to that of SCr and UO.[77] On adjusted analysis, patients in the highest KIM-1 quartile had a 3.2-fold higher odds (95% CI, 1.4–7.4) for a composite outcome compared to patients with the lowest quartile. However, the result was no longer significant when adjusted for multiple factors. In another study by the same authors, KIM-1 was not a significant predictor for RRT, but was a significant predictor for mortality.[72]

Interleukin-18

Interleukin (IL)-18 also has been considered as a candidate biomarker for acute renal injury. IL-18 is a pro-inflammatory cytokine generated by caspase-1-mediated cleavage in injured proximal tubules and released into the urine.[78] It can also enter the urine by glomerular filtration. In animal models, IL-18 has been shown to exacerbate tubular necrosis, and neutralizing antibodies to IL-18 reduced renal ischemic injury in mice.[78] In humans urinary IL-18 levels were measured in 72 individuals, 14 with ATN, 8 with prerenal failure, 5 with urinary tract infections, 12 with CKD, 22 who received a kidney transplant, and 11 healthy control subjects. Patients with ATN had significantly higher urinary IL-18 levels as compared with control subjects and patients with other forms of kidney disease.[66] Similarly, patients who underwent transplantation and had delayed graft function had higher urinary IL-18 levels than patients with prompt graft function. Using samples collected on days 0, 1, and 3 of the Acute Respiratory Distress Syndrome (ARDS) Network trial, urine IL-18 levels of >100 pg per mL were associated with a 6.5-fold increased risk for development of AKI, defined by RIFLE.[52]

Many other factors beside GFR determine biomarker elevation: heterogeneity of clinical settings, underlying patient characteristics, severity of illness, and potential reasons for decreased renal function. It is more likely that a panel of biomarkers will provide a better understanding about the timing, nature, and the severity of an acute renal insult. Further work is clearly needed to inform the time course and performance of AKI biomarkers in various situations, to identify the pathways involved, to define clinical endpoints, including prerenal states, and to improve adjudication of biomarker data with respect to functional changes.[79]

DETERMINING REVERSIBILITY

Although epidemiologic studies have shown that even small increases in SCr are predictive of nonrenal outcomes, SCr remains an insensitive and delayed marker of AKI. A key unanswered question is whether reversible AKI or prerenal AKI is also associated with increased complications and worse outcomes. For decades the differentiation from intrinsic AKI and prerenal AKI was based on urine analysis and microscopy parameters, but could only be confirmed retrospectively by the reversibility of creatinine increase or improvent of urine output. In the era of the new biomarkers new paradigms may arise to answer this question.

Physiology of Reversibility

The traditional classification of AKI includes causes associated with a decrease in renal blood flow (Table 28.4), intrinsic renal parenchymal diseases (Table 28.5), or obstruction of urine flow (Table 28.6). Although obstructive AKI is usually easier to diagnose, prerenal and intrinsic renal causes can be difficult to distinguish in the clinical setting. Another

28.4 Causes of Reversible Acute Kidney Injury

Decreased Intravascular Fluid Volume
- Extracellular fluid loss—burns, diarrhea, vomiting, diuretics, salt-wasting renal disease, primary adrenal insufficiency, gastrointestinal hemorrhage
- Extracellular fluid sequestration—pancreatitis, burns, crush injury, nephrotic syndrome, malnutrition, advanced liver disease

Decreased Cardiac Output
- Myocardial dysfunction—myocardial infarction, arrhythmias, ischemic heart disease, cardiomyopathies, valvular disease, hypertensive disease, severe cor pulmonale

Peripheral Vasodilation
- Drugs—antihypertensive agents
- Sepsis
- Miscellaneous—adrenal cortical insufficiency, hypermagnesemia, hypercapnia, hypoxia

Severe Renal Vasoconstriction
- Sepsis
- Drugs—nonsteroidal anti-inflammatory agents, β-adrenergic agonists
- Hepatorenal syndrome

Mechanical Occlusion of Renal Arteries
- Thrombotic occlusion
- Miscellaneous (emboli, trauma [e.g. angioplasty])

28.5 Renal Causes of Acute Renal Failure

Renal Vascular Disorders
- Vasculitis
- Malignant hypertension
- Scleroderma
- Thrombotic thrombocytopenic purpura
- Hemolytic–uremic syndrome
- Disseminated intravascular coagulation
- Mechanical renal artery occlusion (surgery, emboli, thrombotic occlusion)
- Renal vein thrombosis

Glomerulonephritis
- Postinfectious
- Membranoproliferative
- Rapidly progressive glomerulonephritis (idiopathic, polyarteritis nodosa, systemic lupus erythematosus, Wegener syndrome, microscopic polyarteritis, Goodpasture syndrome, Henoch-Schönlein purpura)
- Drugs

Interstitial Nephritis
- Drugs (penicillin, sulfonamide, rifampin, ciprofloxacin, phenindiones, cimetidine, proton pump inhibitors [omeprazole, lansoprazole], azathioprine, phenytoin, captopril, thiazides, furosemide, bumetanide, allopurinol, nonsteroidal anti-inflammatory drugs including selective cyclooxygenase-2 inhibitors, 5-aminosalicylates)
- Hypercalcemia

Infections
- Nonspecific due to frank septicemia or systemic anti-inflammatory response syndrome
- Specific organisms (Legionella, Leptospira, Rickettsia, Hantavirus, Candida, malaria)
- Specific organ involvement (bacterial endocarditis, visceral abscess, pyelonephritis)

Infiltration
- Sarcoid
- Lymphoma
- Leukemia

Connective Tissue Disease

Tubular Necrosis
- Renal ischemia (prolonged prerenal)
- Nephrotoxins (aminoglycosides, radiocontrast agents, heavy metals, organic solvents, other antimicrobials)
- Pigmenturia (myoglobinuria, hemoglobinuria)
- Miscellaneous

way to approach AKI classification is to ascertain the possibility of reversibility.

Prerenal AKI has been accepted as a reversible form of renal dysfunction, caused by factors that compromise renal perfusion. The term has been used as part of a dynamic process that begins with a reversible condition, the prerenal state, and can progress to an established disease, ATN. Experimental models have largely informed our current understanding of the physiology of the kidney injury associated with prerenal failure. Before the onset of clinically evident prerenal azotemia, the kidney passes through a phase of remarkable compensation called pre-prerenal azotemia.[80] Three main steps are involved in this compensatory mechanism: (1) the cardiac output fraction that reaches the kidney; (2) plasma filtration by the glomerulus (filtration fraction); and (3) proportion of the glomerular filtrate that is reabsorbed by the tubules. Renal blood flow (RBF) depends on the tone of renal vascular resistance (RVR) in relation to systemic vascular resistance (SVR): if the RVR increases in relation to the SVR, the RBF decreases. At reduced levels

28.6 Causes of Postrenal Acute Kidney Injury

Intrarenal (Intratubular)
- Crystal deposition—uric acid, oxalic acid, methotrexate, acyclovir, triamterene, sulfonamides, indinavir, tenofovir
- Protein deposition—light chains, myoglobin, hemoglobin

Extrarenal
- Ureteral/pelvic
- Intrinsic obstruction—tumor, stone, clot, pus, fungal ball, papilla
- Extrinsic obstruction—retroperitoneal and pelvic malignancy, fibrosis, ligation, abdominal aortic aneurysm

Bladder
- Prostate hypertrophy/malignancy
- Stones
- Clots
- Tumor
- Neurogenic
- Medication

Urethral
- Stricture
- Phimosis

of cardiac output, intrarenal factors are triggered, increasing renal arterial vascular tone and, consequently, decreasing the RBF. In order to maintain the intraglomerular pressure, efferent arteriolar resistance increases, preserving the filtration pressure even when the pressure in the afferent arteriolar decreases to levels low enough to cease filtration. Augmented activity of the sympathetic nervous system, RAAS, and vasopressin secretion increases the amount of filtered fluid and Na^+ that are reabsorbed.

These three mechanisms, control of blood flow to the kidney, the filtration fraction, and amount of fluid and solutes reabsorbed by the kidney, are the components responsible for the kidney reserve. However, the efficiency of these mechanisms has limits imposed by structural changes and the severity of the insult. The reserve is diminished by the presence of underlying arterial and intrinsic renal diseases that interfere with the control of renal blood flow, filtration fraction, and reabsorbtion functions, as well as by drugs that interfere with the vascular or neural humoral control of these mechanisms. When these compensatory mechanisms are overwhelmed, a prerenal state is discernible.

The frequency of prerenal azotemia as a cause of AKI varies with the clinical setting. A prospective study by Hou et al.[81] found prerenal azotemia to be the single most common cause of AKI in a general medical-surgical hospital. Liano found that prerenal causes of AKI among the elderly accounted for 48% of community-acquired AKI and 58% of hospital-acquired AKI (Fig. 28.7).[82,83] Brivet observed that in critically ill patients, prerenal causes accounted for 17% of cases of AKI.[84] Prerenal forms of AKI also appear to be common causes of community-acquired AKI and constituted 70% of all such cases as reported by Kaufman and associates.[85]

The terms "reversible AKI" or "prerenal failure" refer to all these different conditions that vary considerably in pathophysiology and course, including intravascular volume depletion, relative hypotension, compromised cardiac output, or hepatorenal syndrome (HRS). Although these terms are usually defined as an elevation of SCr or a reduction of UO that is easily reversible with improved renal perfusion

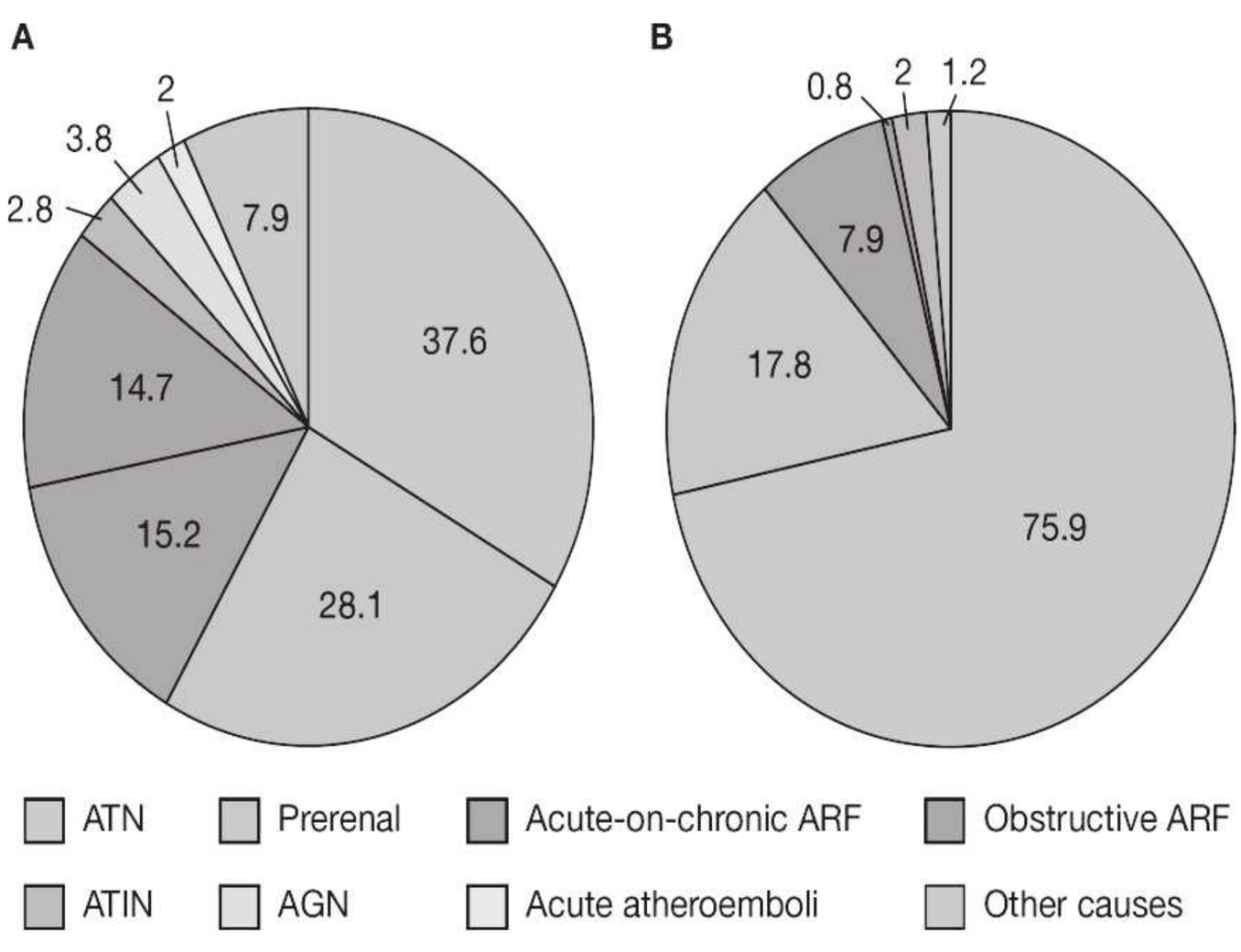


FIGURE 28.7 Percentage distribution of causes of acute renal failure in **(A)** non–intensive care unit (ICU) and **(B)** ICU settings. ICU patients are generally younger, less frequently afflicted by acute-on-chronic renal failure, and have significantly more acute tubular necrosis than the non-ICU group. *AGN*, acute glomerulonephritis; *ARF*, acute renal failure; *ATIN*, acute tubulointerstitial nephropathy; *ATN*, acute tubular necrosis; *ICU*, intensive care unit. (From Liaño G, Pascual J. Acute renal failure. Madrid Acute Renal Failure Study Group. *Lancet*. 1996;347(8999):479; author reply 479.) (See Color Plate.)

pressure, there is no agreement on the amount, nature, and duration of fluid resuscitation needed to eliminate a prerenal state. In most cases, the effect of fluid expansion or hemodynamic effect on renal function is retrospective and frequently evaluated by trial and error. The return of renal function to the previous baseline within 24 to 72 hours is considered to represent a prerenal or reversible condition. Diagnostic strategies have usually been based on demonstrating a fluid responsive change in renal function. The AKIN group recommended the "exclusion of urinary tract obstructions or . . . easily reversible causes of decreased urine output" and application of the diagnostic criteria "following adequate resuscitation when applicable."[17] This modification in the criteria was intended to exclude transient changes in creatinine or UO due to volume depletion or other easily reversible causes of renal hypoperfusion. Although ideally created for prospective application, most studies seeking to validate the criteria were retrospective. In those studies, the exclusion of urinary tract obstruction and prerenal failure are impossible to verify. One small retrospective study attempted to evaluate the outcome of patients that met the adequate resuscitation criteria in comparison to those patients in which data on fluid challenge was not available.[86] Detailed fluid challenge information was available in 123 patients who met AKI criteria. They found that the association of AKI with in-hospital mortality was still significant even when the appropriate fluid challenge requirement was discarded.

Several clinical scenarios are often associated with a potentially reversible or prerenal form of AKI. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with volume depletion, hypoalbuminemia, an edematous disorder, advancing age, underlying chronic renal failure, or recent diuretic use are all contributing factors for prerenal AKI.[87] A similar reversible form of AKI can complicate angiotensin-converting enzyme (ACE) therapy in the presence of decreased RBF from severe bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, and other high-renin, high-angiotensin II states (i.e., edematous states and volume depletion disorders). In these cases ACE inhibition, with a resultant decrease in both renal perfusion pressure and efferent arteriolar constriction, can precipitously decrease GFR. About one third of patients with severe congestive heart failure experience an abrupt rise in SCr concentration following ACE inhibitor therapy.[88] In the setting of heart failure, this increase in SCr following ACE inhibition tends to be mild and readily reversible on discontinuation of the drug.

Although laboratory tests to distinguish reversible prerenal conditions from ATN have been used, these diagnostic parameters present frequent exceptions and the distinction between prerenal and renal causes are frequently not accurate (Fig. 28.8). The plasma (P) urea/creatinine ratio, urine (U) osmolality, U/P osmolality, U/P creatinine ratio, urinary Na level, and fractional excretions of Na (FE_{Na}) are the most frequently used tests. Serum U/P creatinine ratio

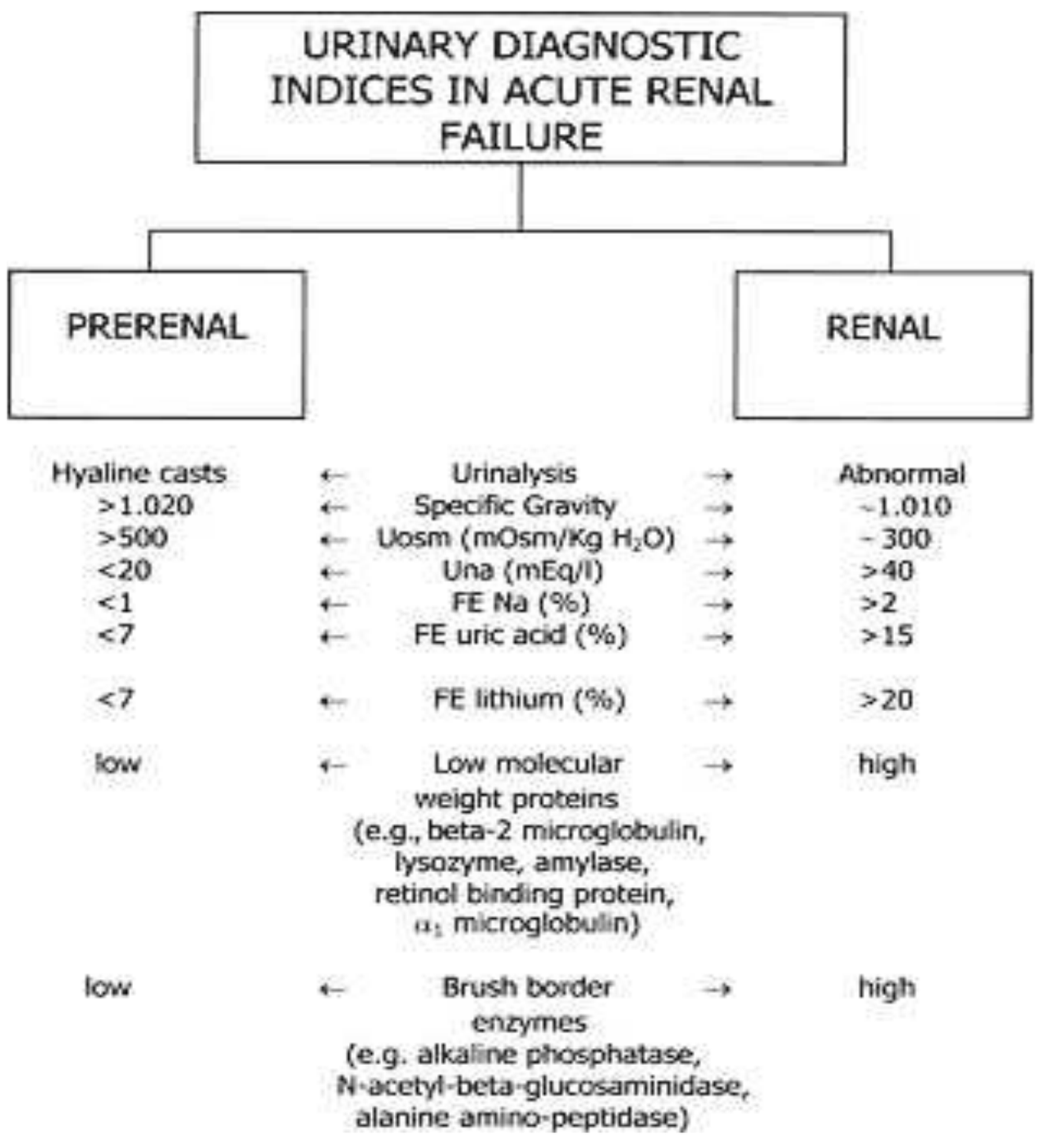


FIGURE 28.8 Urinary diagnostic indices to differentiate between prerenal and renal causes of acute kidney injury.

helps to identify whether the oliguria is a result of water reabsorption (U/PCr > 20) or loss of tubular function (U/PCr <20). In reversible states the reabsorption of sodium is increased, not only from the increase in proximal tubular reabsorption of water, but also by the increase in aldosterone level secondary to hypovolemia. The frequent use of diuretic therapy limits the value of FE_{Na}. The fractional excretion of urea (FE_{UN}) can be helpful in these cases. FE_{UN} relates inversely to the proximal reabsorption of water; urea reabsorption leads to a decrease in FE_{UN} and an increase in the BUN/creatinine ratio. Carvounis et al.[89] found that FE_{UN} has a high sensitivity (85%), a high specificity (92%), and a high positive predictive value; in that study a FE_{UN} less than 35% was associated with a 98% chance of reversible failure. Still, there are limitations for the use of FE_{UN}. In osmotic diuresis and with the use of mannitol or acetazolamide, the proximal tubular reabsorption of salt and water is impaired, so there can be an increase in FE_{UN} even in states of hypoperfusion. The same can occur when a patient is given a high protein diet or presents with excessive catabolism. Urinary osmolality is also used to evaluate the urinary concentration ability, a function that becomes impaired in the early process of tubular dysfunction. A value greater than 500 mOsm per kg indicates that tubular function is still intact, although there are also some considerations about this index; a low protein diet or low protein absorption by intestinal edema can impair the concentration ability of the urine and show a low osmolality even in reversible states.

There are some promising new biomarkers for AKI that may be helpful in distinguishing between reversible and established AKI.[64,69,90] During the reversible state, the persistent vasoconstriction associated with metabolic changes and inflammation promotes the release of cell functional markers that can be detected in the blood and urine. However, at the current time, there are no specific markers representing reversible conditions.

Obstruction to Urine Flow

Obstruction of urine flow is generally considered a less common cause of AKI. In several series, obstructive uropathy is encountered in 2% to 10% of all cases in AKI.[83,84] However, obstructive uropathy is more common in selected patient populations, such as the very young or older men with prostatic disease, and patients with a single kidney or intra-abdominal cancer, particularly pelvic cancer. Obstructive uropathy is most frequently encountered in community- and hospital-associated AKI and is less common in ICU-related AKI.[82,83] For example, obstructive uropathy constitutes 20% to 40% of all community-acquired AKI. Finally, the cause of obstructive uropathy is often amenable to therapy. Thus, obstructive uropathy should be considered in each case of AKI.

Obstruction of urinary flow can occur anywhere from the kidneys to the urethral meatus. Certain points along this path are more susceptible to obstruction. The three points of narrowing along the ureter include the ureteropelvic junction, the crossing of the ureter over the area of the pelvic brim, and the ureterovesical junction. The cause of obstruction of urine flow can be classified as intrarenal or extrarenal (Table 28.6). Intratubular deposition of either crystalline or proteinaceous material can increase intratubular pressure, thereby decreasing effective glomerular filtration pressure. For example, intratubular precipitation of uric acid can cause tubule obstruction and AKI. Acute uric acid nephropathy is most often seen following chemotherapy for leukemias and lymphomas. In this setting, the liver converts the purine load generated by cytolysis into uric acid. The high filtered load of uric acid and tubular reabsorption combine to produce high tubular concentrations of soluble urate and uric acid. Acidification of tubular fluid converts urate to uric acid, which can crystalize and occlude tubular lumens.

Abrupt exposure of the kidneys to high filtered loads of other insoluble crystalline substances can also cause an intrarenal form of obstructive uropathy. For example, AKI associated with calcium oxalate crystalluria can accompany ethylene glycol ingestion, administration of the anesthetic agent methoxyflurane, chronic pancreatitis, and use of gastrointestinal lipase inhibitors.[91–94] Administration of high doses of methotrexate can be associated with AKI, possibly owing to intratubular precipitation of the insoluble 7-hydroxy metabolite of methotrexate.[95] Other crystalline substances that can potentially precipitate within renal tubules and lead to AKI include acyclovir, triamterene, sulfonamides, and protease inhibitors such as indinavir.[96]

Another cause of intratubular obstruction is the deposition of immunoglobulin light chains in plasma cell dyscrasias. Immunoglobulin light chains are low molecular weight proteins that are filtered through the glomerulus and reabsorbed into the proximal tubular epithelium by initially binding to a heteromeric receptor complex composed of megalin and cubilin.[97] Saturation of this receptor-mediated endocytotic process results in the presence of free light chains in the distal nephron and urine. Nephrotoxicity of the metabolism of monoclonal light chains causes tubulointerstitial nephritis and cast nephropathy (also known as "myeloma kidney"), resulting in AKI and progressive CKD from tubular obstruction.[97]

Extrarenal lesions are the most common cause of postrenal AKI and are listed in Table 28.6. Several factors determine renal response to extrarenal obstruction. The site, degree, and rapidity of onset of obstruction are all important. Without a complicating infection, substantial improvement in renal function can follow decompression of the urinary tract after several days of complete obstruction. In men, prostatic obstruction is by far the most common cause of postrenal AKI because of its critical location at the bladder outlet. Obstruction of the upper urinary tract is a less common cause of AKI because it requires simultaneous obstructions of both ureters or unilateral ureteric obstruction with either absence of or severe disease in the contralateral kidney. Intraureteric obstruction can be due to stone, released necrotic papillae, tumor, pus, blood clots, and fungal balls. Papillary necrosis can occur in the

setting of sickle cell disorders, chronic urinary tract infections, analgesic abuse, and obstructive uropathy. Extraureteric lesions producing obstruction include retroperitoneal fibrosis, adenopathy, and tumors. Retroperitoneal fibrosis is often idiopathic but may be encountered in response to retroperitoneal neoplasia as well as in the setting of some pharmacologic agents (methysergide, methyldopa, β-blockers), prolonged peritoneal dialysis, and some connective tissue diseases. It has been reported that a high frequency of AKI occurs because of prostatic carcinoma in males and pelvic carcinoma (predominantly cancer of the cervix) in females causing ureteric occlusion. Less commonly encountered causes of extrinsic ureteric obstruction include inflammatory bowel disease (predominantly right-sided obstruction), an inflammatory reaction resulting from a leaking abdominal aortic aneurysm, and the late stages of pregnancy.

Acute obstruction can also be related to use of pharmacologic agents with potential anticholinergic effects (e.g., tricyclic antidepressants, phenothiazines, antihistamines) and cold remedies containing α-adrenergic agents (e.g., phenylpropanolamine) often precipitate acute urinary retention by impairing detrusor function and enhancing bladder sphincter tone, respectively.

PROLONGED OR SUSTAINED ACUTE KIDNEY INJURY

A variety of renal disorders can lead to a prolonged or sustained AKI (Table 28.5). In hospitalized adults in whom reversible and obstructive causes have been excluded, AKI is often caused by ATN. By contrast, in an outpatient setting in which reversible and obstructive causes have been excluded, other renal parenchymal diseases more often cause AKI.

Three major categories of insults are associated with ATN: prolonged renal ischemia, nephrotoxins, and pigmenturia (myoglobinuria and hemoglobinuria). Patients with ATN frequently present with more than one insult and several experimental studies in animal models of AKI demonstrate that multiple renal insults such as fever, bacteremia, endotoxemia, relative hypotension, and aminoglycoside exposure contribute to decrements in renal function with resulting AKI. This is referred to as multifactorial AKI.

The most common predisposing factor in the development of ATN appears to be renal ischemia resulting from a functional or structural reduction in renal perfusion.[10,83,98] Sepsis, and particularly septic shock, has assumed an ever-increasing role as a major predisposing factor in the occurrence of ATN.[10,99] Nephrotoxins are involved in about 20% of all cases of ATN.[10,83,98] Contemporary nephrotoxins commonly encountered include the aminoglycoside antimicrobial agents, radiographic contrast materials, NSAIDs, and antineoplasic drugs (Table 28.7). A high proportion of patients with AIDS develop nephrotoxicity from drugs used to manage HIV.

28.7 Factors Predisposing the Kidney to Nephrotoxicity

Drug-Related	Patient-Related
Concentration of the drug through reabsorptive and secretive processes	Preexisting renal dysfunction
High number of transporters result in high intracellular concentrations	Dehydration
Large luminal membrane surface area	Diabetes mellitus
Large biotransformation capacity	Exposure to multiple nephrotoxins

Diagnostic Approach

There are numerous causes of AKI, some of which are amenable to specific therapeutic interventions. For these interventions to be effective they must be applied early in the course of the disease process, preventing further deterioration of the renal function as mortality and complications of AKI appear to be proportional to its severity.[19] For example, Chertow et al. showed a 6.5-fold increase in the odds of death for patients with a 0.5 mg per dL increase in SCr.[100] In pediatric patients with acute decompensated heart failure, Goldstein et al. found that a rise in SCr of 0.3 mg per dL or more was associated with a sevenfold increased risk of in-hospital death.[101] Additionally, several studies have shown that the change in severity stage of AKI (AKIN from RIFLE) is associated with an incremental risk for mortality.[14,19,21,102] An early diagnosis and accurate assessment of AKI severity is essential to develop approaches for earlier intervention, correct reversible factors, and mitigate the downstream effects of AKI.

Chart Review, History, and Physical Examination

Meticulous chart analysis to determine recent clinical events possibly associated with the development of AKI is fundamental (Fig. 28.9). A history with regard to prescription drugs, over-the-counter agents, and herbal preparations, as well as possible environmental exposure, is critical as nephrotoxins are frequently contributing factors to the development of AKI. The relationship between medication exposure and AKI may not be readily apparent in some cases, thus a detailed history should always be performed. The presence of signs and symptoms of sepsis or heart failure, and symptoms related to the genitourinary tract (urine

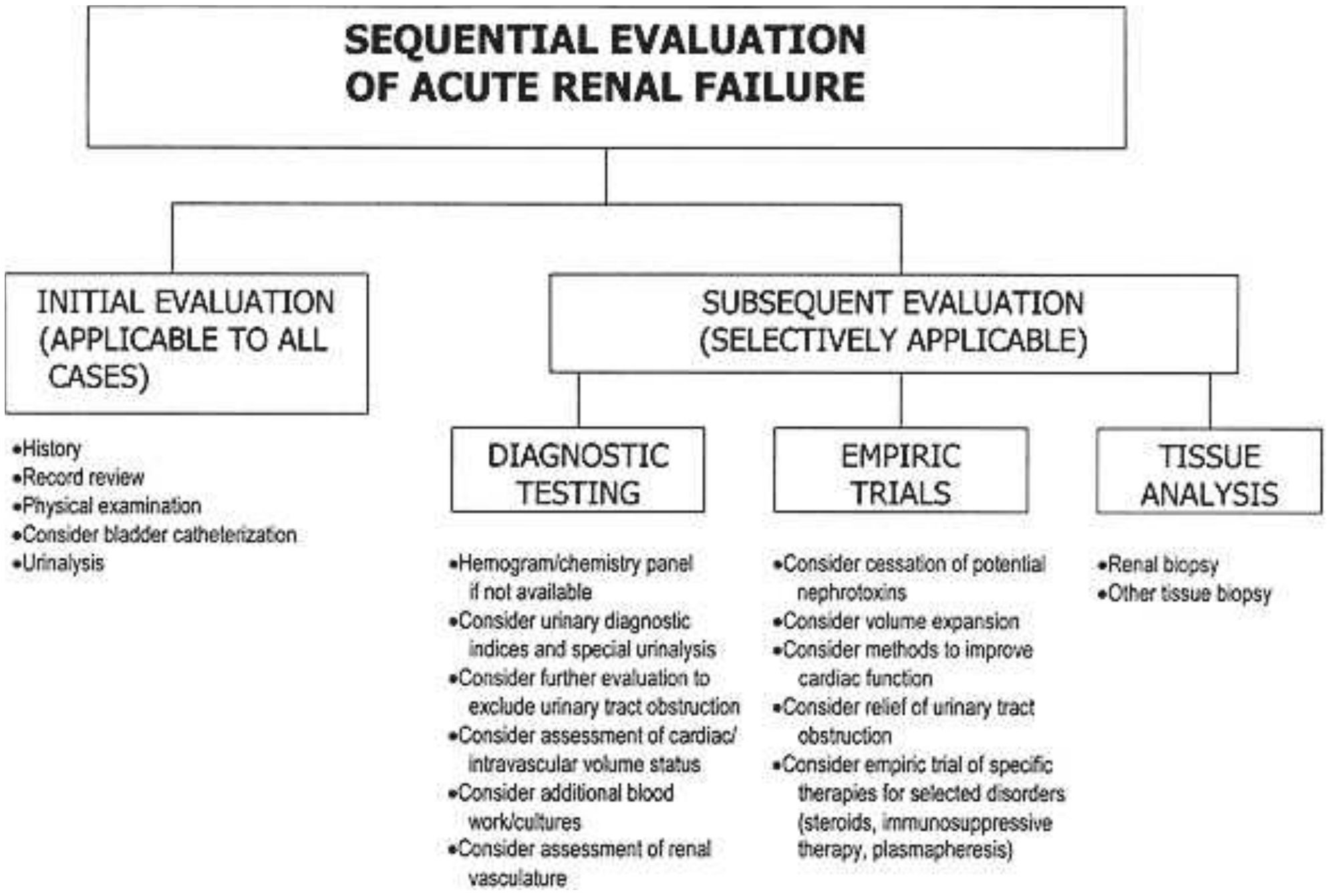


FIGURE 28.9 Suggested sequential diagnostic evaluation to determine the cause of acute kidney injury.

output, pyuria, dysuria, hematuria, and flank or abdominal pain) can provide helpful diagnostic information. Intense thirst, salt craving, orthostatic syncope, and muscle cramps often are symptoms of extracellular fluid volume depletion. Examination of serial vital signs, hemodynamic data, intake and output, and daily weight can provide important data regarding the cause of AKI. A weight change of greater than 0.25 to 0.50 kg per day indicates gain or loss of salt and/or water. Recording of serial renal functional data and correlation of any deterioration in renal function with clinical events such as those altering systemic hemodynamics and use of potential nephrotoxins often are of great diagnostic value. Physical examination can be of value in determining the presence or absence of prerenal and postrenal causes of AKI, as well as the presence of a systemic disorder that could result in a renal cause of AKI. The effect of either loss or sequestration of extracellular fluid volume on systemic hemodynamic responses depends on several variables, including the composition and rate of fluid loss and the underlying health state of the patient.

Physical examination must also include palpation for determining the state of peripheral circulation, renal size, and the possibility of abdominal aortic aneurysms. Palpation or percussion of the suprapubic area is necessary to detect bladder distention, and rectal and pelvic examinations are needed to detect prostatic and pelvic disorders. Examination of the skin may reveal palpable purpura suggestive of vasculitis; lower extremity evaluation may reveal livedo reticularis and evidence of emboli, suggesting atheroembolic disease. It is beyond the scope of this chapter to detail all the physical findings that can be associated with causes of AKI; however, the presence of neurologic or pulmonary disease, fever, skin lesions, joint abnormalities, or diffuse lymphadenopathy suggests the presence of a systemic disorder associated with AKI.

Laboratory

Blood Urea Nitrogen

Elevations in BUN are dependent on the nitrogen intake, the degree of renal impairment, and the degree of protein catabolism. In the noncatabolic patient with mild renal impairment, daily BUN usually increases <10 to 15 mg per dL per day and SCr <1.5 mg per dL per day. High catabolic states and high-protein diets are associated with greater urea nitrogen production that can exceed 50 mg per dL.

Another condition associated with a BUN increase not proportional to the rise in SCr level and fall in GFR is the presence of decreased intravascular effective volume. Normally, the usual BUN:SCr ratio is about 15:1 and the BUN and SCr increases by 10 to 15 and 1.0 to 1.5 mg/dL/day, respectively, in the absence of GFR. In situations characterized by decreased glomerular perfusion pressure, such as heart failure, BUN can increase independently from SCr. Elevations

in BUN are independent from SCr levels, and these two parameters are a reflection of the severity of renal dysfunction, and actually a consequence of two distinct pathologic processes.[36–38] The activation of RAAS and the sympathetic nervous system are responsible for decreasing the glomerular perfusion pressure and GFR. The increment in vasopressin levels upregulates aquaporin-2 expression and increases water reabsorption. Urea, in contrast to SCr, is not secreted but reabsorbed by the renal tubules. The increased reabsorption of sodium and water, rather than the reduced GFR, enhances reabsorption of urea and increases BUN levels. Thus, BUN levels and BUN/creatinine ratio could be a more effective way to assess circulatory volume than GFR, which is regulated by the pressure difference between glomerular afferent and efferent arterioles.[39] In heart failure, and possibly in other settings where underfilling is part of the pathophysiologic process, the rise in BUN greater than any fall in GFR is a marker of the neurohumoral axis activation.[40]

In selected circumstances it may not be clear if an elevated BUN:SCr ratio is due to an acute or chronic process. In these settings, a review of previous records is helpful. Although the test is not widely avilable, measurement of carbamylated hemoglobin can be helpful. Hemoglobin potentially undergoes nonenzymatic carbamylation of its terminal valine. Thus, similar to the hemoglobin A1C value as an index of blood sugar control, the level of carbamylated hemoglobin is an indicator of the degree and duration of elevated BUN.[103,104] A carbamylated hemoglobin level greater than 80 to 100 μg carbamyl valine per gram hemoglobin suggests the diagnosis of chronic rather than ARF.[105,106]

Serum Creatinine

Clinicians usually follow daily SCr concentrations to assess whether GFR is increasing, decreasing, or constant in patients with AKI. The SCr concentration, however, is dependent on creatinine production, volume of distribution, and renal elimination. However, in patients with AKI, changes in GFR often correlate poorly with changes in SCr concentration. In AKI, three main factors influence the estimation of kidney function: the actual GFR, fluctuations in creatinine production, and fluid balance.[33] Moran and Myers[107] demonstrated this in several patterns of AKI (abrupt and large, slow and progressive, and stepwise). They developed a simple, computerized model of creatinine kinetics in patients with postischemic AKI to calculate GFR based on SCr concentration corrected for changes in creatinine volume of distribution. They suggested that changes in GFR are difficult to evaluate using SCr concentration alone in the setting of AKI.[33]

Jelliffe developed an equation to estimate GFR in patients with unstable (nonsteady state) kidney function that considered fluctuations in kidney function and creatinine production without requiring timed urine collection.[108] The Jelliffe equation is based on the concept that daily changes in SCr depend on the difference between creatinine production and excretion. Bouchard et al. demonstrated that the GFR by Jelliffe correlated best with urinary creatinine clearances.[109] In an ICU cohort the eGFR by Cockcroft–Gault, Modification of Diet in Renal Disease, and Jelliffe overestimated urinary creatinine clearance in 80%, 33%, and 10%, respectively. The relative overestimation of GFR in AKI with both Cockcroft–Gault and MDRD was more prominent when baseline GFR was higher.

Fluid administration is a common and required component of the management of critically ill patients and has recently focused on goal-directed resuscitation with early volume expansion in the ICU course. These strategies frequently result in a relative increase in body weight of 10% to 15% or more, sometimes doubling the total body weight in a short period of time.[110] The fluid accumulation increases the extracellular fluid (ECF), altering the volume of distribution of SCr, and resulting in potential overestimation of the level of kidney function.[34] The masking of AKI severity by volume expansion may be especially problematic in settings where the SCr is rising relatively slowly owing either to lower creatinine generation (e.g., as might be expected in the elderly or patients with less muscle bulk) or to more modest overall injury.

Urine Microscopy

Urinary microscopy (UM) is an integral part of the clinical evaluation of patients with kidney disorders and is frequently utilized to differentiate some clinical conditions (e.g., nephrotic syndrome, urinary tract infection, nephritic syndrome). Drug toxicity has also been assessed by UM, as in the case of indinavir, acyclovir, and amoxicillin, associated with variable degrees of leukocyturia, crystalluria, and cellular casts.[96,111–113]

In the case of AKI, UM has traditionally been used as a tool to differentiate prerenal AKI and ATN. Sediment containing few formed elements or only hyaline casts strongly suggests prerenal azotemia or obstructive uropathy. With ATN, brownish-pigmented cellular casts and many renal tubular epithelial cells are observed in more than 75% of patients. Sufficient red blood cells to cause microscopic hematuria are traditionally thought to be incompatible with a diagnosis of ATN and usually result from glomerulonephritis or structural renal disorders (stones, tumor, infection, or trauma). Red blood cell casts suggest the presence of glomerular or vascular inflammatory diseases of the kidney and rarely, if ever, occur with ATN. Red blood cell casts, however, can be seen rarely in acute interstitial nephritis. The presence of large numbers of polymorphonuclear leukocytes, singly or in clumps, suggests acute diffuse pyelonephritis or papillary necrosis. In allergic tubular-interstitial nephritis eosinophilic casts on Hansel's stain of urine sediment may be diagnostically helpful.[114–116] Eosinophiluria may be also present in some forms of glomerulonephritis and in atheroembolic renal disease but is rarely encountered in ATN.[117] The combination of brownish-pigmented granular casts and positive occult blood tests on urine in the absence of hematuria indicates either hemoglobinuria or myoglobinuria. In AKI, the finding of large numbers of "football-shaped" uric acid

crystals in fresh, warm urine may suggest a diagnosis of acute uric acid nephropathy, whereas the finding of large numbers of "back-of-envelope–shaped" oxalic acid suggests ethylene glycol toxicity.[118] Other agents (e.g., indinavir, sulfadiazine, acyclovir, and methotrexate) also can induce AKI with characteristic crystal appearance on urinalysis.[112,118] The presence of broad casts (defined as more than three white blood cells in diameter) suggests chronic renal disease.

Recently, two different groups have revised the clinical value of performing UM.[119,120] In a pilot study, Chawla et al. developed an AKI cast-scoring index to standardize urine-sediment. The score precision was evaluated in 30 patients with a clinical syndrome compatible with ATN with an interobserver index of 99.8 ± 0.29%, and a coefficient of variation of 1.24%. Urine-sediment was further correlated with outcomes in 18 patients with ATN. The authors found that renal recovery was worse in those patients with a higher cast scoring index (2.55 ± 0.9 vs. 1.7 ± 0.79; P = .04), and area under the ROC curve of the cast scoring system to predict nonrenal recovery was 0.79. In another study, Perazella et al. proposed a different scoring system for differentiating ATN from prerenal AKI (Table 28.8).[120] Using the final AKI diagnosis at discharge as a gold standard, UM at the day of nephrology consultation was highly predictive of ATN. The odds ratio for ATN incrementally increased with a higher score. In patients with initial diagnosis of ATN, any granular casts (GCs) or renal epithelial tubular cells (RETCs) (score 2) resulted in a PPV of 100% and a NPV of 44%. The lack of RTECs or GCs in patients with initial diagnosis of prerenal AKI had a sensitivity of 0.73 and specificity of 0.75 for the final diagnosis of

28.8 Recent Studies Evaluating Urinary Microscopy in Acute Kidney Injury

Reference	Standardized Method of Sample Preparation	Score System Used[a]
Bagshaw et al.[b]	None	Description of common findings in urine sediment of patients with sepsis of 7 studies included (common presence of muddy brown or ECCs, RTECs, and variable trace hematuria and pyuria)
Chawla et al.[c]	**Volume collected:** 10 mL **Centrifugation process:** 5 minutes at 2,000 rpm **Supernatant:** decanted (9.5 mL) **Residual sample for analysis:** 0.5 mL **Resuspend:** by hand Pipette use to dispense 1 drop of sediment to a glass slide and 24 × 30 mm coverslip gently applied	**Grade 1**: None (no evidence of GCs or ECCs) **Grade 2** : Rare (rare GCs or ECCs; at least 1 GC or ECC seen on the entire slide, but 10% of LPFs) **Grade 3**: Moderate (many GCs or ECCs, but not seen on every LPF; casts seen on >10% but <90% of LPFs) **Grade 4**: Sheets (sheets of muddy brown cast; GCs or ECCs seen on >90% of LPFs)
Perazella et al.[d]	**Volume collected:** 10 mL **Centrifugation process:** 5 minutes at 2,000 rpm **Supernatant:** removal by suction (9.5 mL) **Residual sample for analysis:** 0.5 mL **Resuspend:** by hand Pipette use to dispense 1 drop of sediment to a glass slide and coverslip gently applied	**Score 1**: RTECs 0 and GCs 0 **Score 2** : RTECs 0 and GCs 1–5 or RTECs 1–5 and GCs 0 **Score 3**: RTECs 1–5 and GCs 1–5 or RTECs 0 and GCs 6–10 or RTECs 6–20 and GCs 0
Perazella et al.[e]	**Volume collected:** 10 mL **Centrifugation process:** 5 minutes at 2,000 rpm **Supernatant:** removal by suction (9.5 mL) **Residual sample for analysis:** 0.5 mL **Resuspend:** by hand Pipette use to dispense 1 drop of sediment to a glass slide and coverslip gently applied	**RTECs (per HPF)** 0 (0 points) 1–5 (1 point) ≥6 (2 points) **GCs (per LPF)** 0 (0 points) 1–5 (1 point) ≥6 (2 points)

28.8 Recent Studies Evaluating Urinary Microscopy in Acute Kidney Injury (continued)

Reference	Differential Diagnosis Pre-renal vs. ATN	Prediction of Outcomes	Comments
Bagshaw et al.[b]	Not assessed	Not assessed	Only 7 studies (26%) from the 27 included in the systematic review reported urinary microscopy or sediment findings.
Chawla et al.[c]	Not assessed	Nonrenal recovery (need of RRT or death while SCr trend was still rising) **Nonrecovery:** CSI score 2.55 ± 0.93 **Recovery:** CSI score 1.57±0.79 **ROC** area under the curve for CSI was 0.79	Standardized urine sediment processing method Score system for predicting outcomes
Perazella et al.[d]	**Score 1:** OR 9.7 (95% CI, 5.3–18.6) **Score ≥2:** OR 74 (95% CI 16.6–329.1)	Not assessed	Standardized urine sediment processing method Score system for differential diagnosis
Perazella et al.[e]	Score not employed for differential diagnosis	Worsening AKI (increase in AKIN stage, need of RRT, or in-hospital death) adjusted RR compare to 0 points. **1 points** → 3.4 (95% CI 1.3–6.5) **2 points** → 6.6 (95% CI 3.4–9.1) **≥3 points** → 7.3 (95% CI 3.8–9.6)	Standardized urine sediment processing method Score system for predicting outcomes

[a]Reference test use as a gold standard for diagnosis of acute kidney injury.
[b]Bagshaw et al. (2006): No gold standard used for assessing urinary sediment performance, study only resumes common findings in urine sediment of patients with sepsis.
[c]Chawla et al. (2008): Clinical syndrome consistent with ATN determined by the renal consult service.
[d]Perazella et al. (2008): Final diagnosis of the patient type of AKI at discharge (ATN, Pre-renal AKI, or other) as determined by renal consult service.
[e]Perazella et al. (2010): The same as in Perazella et al. (2008).
AKI, acute kidney injury; AKIN, acute kidney injury network; ATN, acute tubular necrosis; SCr, serum creatinine; RRT, renal replacement therapy; ECCs, epithelial cellular casts; GCs, granular casts; RTECs, renal tubular epithelial cells; LPH; low power field; HPF, high power field; RR, risk ratio; OR, odds ratio; CI, confidence interval; CSI, cast scoring index.

From Claure-Del Granado R, Macedo E, Mehta RL. Urine microscopy in acute kidney injury: time for a change. Am J Kidney Dis. 2011;57(5):657–660.

ATN. A scoring point system of UM findings was used to predict adverse outcomes.[121] Correlation of the urinary-sediment score and AKIN stage at nephrology consultation was demonstrated, and the score was associated with a higher risk of worsening AKI in a dose-dependent manner.

Urinary Chemical Indices

Since the 1940, the concentrations of sodium (U_{Na}) and chloride (U_{Cl}) in the urine have been known to be high during established phases of ATN. Although the accuracy of U_{Na} alone in determining the cause of AKI was limited, the renal failure index ($U_{Na} \div$ U/P creatinine) or the fractional excretion of sodium (FE_{Na} or $U/P_{Na} \div$ U/P creatinine $\times$ 100) was found to have a high degree of accuracy in differentiating between reversible prerenal azotemia and ATN. However, there are several caveats when using spot urine chemistries as a diagnostic tool to evaluate the cause of AKI. Despite widespread, routine use, no study has demonstrated that knowledge of these indices either changes management or improves outcome of AKI.

Nearly all studies of spot chemistries have been performed at a single time point often relatively late in the course of AKI. The lack of serial data is important because AKI is a dynamic process. During the early phases of AKI, renal tubular function is intact. Later, cell injury may result in loss of tubular cell polarity. The resulting urine chemistries, therefore, are dependent on the phase of the course in which they were obtained. This may limit the sensitivity and specificity of urine chemical indices. For example, the early course of AKI occurring in the setting of sepsis,

radiocontrast exposure, rhabdomyolysis, and NSAID use is often associated with renal vasoconstriction, hypoperfusion of the kidney, and low FE_{Na}.[122] Later in the course, the FE_{Na} often increases, if tubular necrosis occurs.

Two other points deserve emphasis with regard to use of urine chemistries as an AKI diagnostic tool. Early in the course of urinary tract obstruction, in some patients with nonoliguric ATN, and in some vascular/glomerular disorders (acute glomerulonephritis, vasculitis, thrombotic thrombocytopenic purpura) urinary chemical indices can be indistinguishable from those seen with prerenal AKI. Conversely, several acute renal parenchymal disorders (e.g., interstitial nephritis, severe ischemic nephropathy, and exacerbations of chronic renal failure) can be associated with urine chemical parameters indistinguishable from ATN, suggesting a lack of specificity. Finally, it is important to acknowledge that potentially reversible prerenal AKI with an $FE_{Na} > 1\%$ occurs in selected settings such as recent diuretic use, bicarbonaturia, salt-wasting nephropathy, glycosuria, and mineralocorticoid deficiency. In the setting of prerenal AKI associated with bicarbonaturia, the urinary chloride concentration is low, confirming a prerenal state.[123] In the setting of prerenal AKI associated with diuretic use, the fractional excretion of trace lithium, urea nitrogen, or uric acid continues to be low.[124] Although urine chemical indices are most often used as diagnostic adjuncts in patients with AKI, they may also provide prognostic information. Some studies suggested that in oliguric patients with AKI lower values for FE_{Na} and higher values for U/P osmolality can predict a high likelihood of a response to diuretics.[125]

Miscellaneous Tests

In some circumstances the cause of AKI may not be evident after chart review, history, physical examination, and urinalysis. In some cases a review of the hemogram may be helpful. A peripheral blood smear that reveals rouleaux formation may suggest the presence of a plasma cell dyscrasia. Eosinophilia is compatible with allergic interstitial nephritis, atheroembolic disease, and polyarteritis nodosa. A microangiopathic picture with thrombocytopenia suggests vasculitis, malignant hypertension, the HELLP syndrome, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura. The presence of coagulopathy can suggest either disseminated intravascular coagulation or an antiphospholipid antibody syndrome as the cause of AKI. If glomerulonephritis is a diagnostic possibility, then the presence of antineutrophilic cytoplasmic antibodies may suggest a diagnosis of either Wegener granulomatosis (primarily a cytoplasmic pattern) or pauci-immune glomerulonephritis (primarily a perinuclear pattern). Antibodies to glomerular basement membrane are strongly suggestive of Goodpasture syndrome, whereas antinuclear antibodies and antibodies against DNA suggest the presence of systemic lupus erythematosus. The presence of cryoglobulins may point to the presence of circulating immune complexes, a plasma cell disorder, or primary cryoglobulinemia.

Imaging

Ultrasonographic evaluation of the kidney can also help in the diagnosis of AKI. Ultrasound is an excellent modality for structural imaging as it is possible to detect renal parenchyma size, scarring, fibrosis, and polycystic kidneys. The presence of small kidney size strongly supports a diagnosis of chronic renal disease and may also help to differentiate acute from chronic renal failure. The echogenicity of the cortex can be assessed with a hyperechoic cortex (normal cortex is hypoechoic to liver), present in most cases of chronic renal failure, adult polycystic kidney disease being the notable exception. Noncontrast computed tomographic (CT) and magnetic resonance imaging (MRI) scans analyze renal structure and renal artery calcification. Other functional studies, such as mercaptoacetyltriglycine (MAG3) and diethylene triamine pentaacetic acid (DTPA), evaluate renal perfusion, uptake, and excretion of a tracer.

A further role of imaging is to determine the number of present and functioning kidneys. For ARF to occur in previously normal kidneys, the underlying cause must be a bilateral process, or a single functioning kidney must be compromised.

Kidney ultrasonography is most commonly ordered in the setting of AKI to rule out urinary tract obstruction. Although renal ultrasonography is a safe and noninvasive test, because obstruction is a relatively uncommon cause of hospital-acquired AKI, the majority of ultrasonography results obtained are negative. In fact, hydronephrosis (HN), the evidence of obstruction on imaging, is only identified on renal ultrasound in 1% to 10% of patients with AKI.[10,126] Licurse et al.[127] sought to create a stratification system that would help clinicians ascertain the risk of renal obstruction among those with AKI. The idea was to improve the probability of a positive finding on renal ultrasound. The authors identified multiple risk factors for hydronephrosis: history of hydronephrosis, history of abdominal or pelvic cancer, prior pelvic surgery, or a single functioning kidney. Patients with a history of heart failure, granular casts on urinalysis, elevated leukocyte count, documented hypotension, or exposure to aspirin, diuretics, or vancomycin during hospitalization were less likely to have hydronephrosis.[127] Patients in the ICU also have a lower incidence of obstruction.

Obstructed kidneys are typically normal sized with dilated ureters, renal pelvis, and calyceal systems. The urine-filled structures appear as anechoic areas with posterior acoustic enhancement. Ureter and renal pelvis can be dilated without being obstructed, mainly after previous obstruction that leaves a residual dilated collecting system, or as an anatomic variant (enlarged extrarenal pelvis). False negatives can occur in the hyperacute setting if the renal collecting system has not had time to dilate, or if associated with retroperitoneal fibrosis. Noncontrast CT scan is the gold standard for detecting ureteric calculi. The ureters can usually be traced between the kidney and bladder, and a hyperdense stone can be seen at the distal site of hydroureter. More than

99% of renal calculi are radiopaque on CT scan; however, xanthine calculi may be radiolucent and stones associated with indinavir are radiolucent. The obstructed kidney is typically edematous (i.e., swollen) with perirenal stranding. A noncontrast study can usually detect many extrinsic compressing masses, such as retroperitoneal tumors or cervical or colon carcinomas, that may produce bilateral obstruction. Scintigraphic imaging with either Tc-99m-MAG3 or Tc-99m-DTPA can detect ureteric obstruction and the negative predictive value of nuclear medicine scanning is extremely high.

In ATN, ultrasounds will usually show enlarged kidneys with a smooth contour caused by interstitial edema. The cortex can present normal echogenicity with either a normal or hypoechoic medulla. The renal arteries can also be evaluated for the renal index (RI), which is an objective measure of the resistance to renal perfusion. RI is defined as (systolic velocity minus diastolic velocity) divided by systolic velocity, and has been heavily investigated to determine whether elevation in RI can differentiate ATN from renal hypoperfusion not yet complicated by ATN. Unfortunately, RI has inadequate specificity for routine clinical use. The examination of choice in suspected ATN is a MAG3 nuclear medicine study. Scintigraphic imaging examinations in ATN using Tc-99m-MAG3 demonstrate relatively well-preserved on-time renal perfusion and delayed tracer uptake, often with a continuing activity accumulation curve. Excretion of tracer into the collecting system is delayed and reduced, but there is no obstruction to drainage of the collecting systems.

In suspected glomerulonephritis or acute interstitial nephritis, the "gold standard" diagnostic test is a renal biopsy. The main role of imaging is to detect structural signs of chronic renal disease and to exclude other causes of ARF. MAG3 studies will show poorly functioning kidneys, but will not show accumulation pattern or obstruction to drainage. Edema can sometimes be demonstrated with ultrasound, manifesting as hypoechoic large kidneys.

Renal Biopsy

A renal biopsy is rarely undertaken but should be considered in the setting of AKI in the presence of: (1) no obvious cause of AKI, (2) either extrarenal clinical evidence or a history of systemic disease, (3) heavy proteinuria and persistent hematuria, (4) marked hypertension in the absence of volume expansion, (5) prolonged (>2 to 3 weeks) oliguria, and (6) anuria in the absence of obstructive uropathy. In clinical practice, most nephrologists choose to biopsy when they are not confident of the cause of the AKI or when the renal injury has an obscure etiology. In a significant proportion of patients diagnosed with AKI, the clinical context suggests the etiology with a reasonable degree of certainty. In other less clear cases the lack of efficient therapeutic options coupled with the risks of a biopsy decreases the likelihood that the clinician will perform the procedure. However, the development of AKI is often multifactorial, and some other causes of AKI may be misclassified as ATN.

Several studies have examined the clinical utility of renal biopsy in the setting of AKI.[128,129] Rivera et al. obtained data from 9,378 cases with native biopsy-proven renal diseases between 1994 and 2001, investigating clinicopathologic correlations. Acute renal failure was an important cause for performing a kidney biopsy: 12% in that cohort. The majority of the biopsies were in adults and elderly patients, predominantly with the suspicion of vasculitis and crescentic glomerulonephritis (GN).[129] In an Italian survey similar results were found: 34.1% frequency of vasculitis and crescentic GN in 1,059 renal biopsies of patients with AKI.[130] In Baltimore, 259 renal biopsies of adults older than 60 years with ARF showed similar results: 35.2% of the diagnoses were crescentic GN.[131] However, these studies included mostly patients with active urinary sediment, a selection bias resulting from clinical practice of biopsy indication in AKI. In most AKI patients, clinical evaluation eliminates prerenal and postrenal causes of AKI, and the results of the biopsies show what we would find when performing biopsy in AKI patients who are thought not to have ATN.[132] Another issue is determining the number of patients clinically diagnosed with ATN who actually have another disease other than AKI. Most importantly, it is necessary to determine the number of patients with treatable forms of AKI that are not being identified.

Several studies have suggested significant discordance between prebiopsy and postbiopsy diagnoses in the setting of AKI. Haas et al. studied the elderly and found the clinical diagnosis to be incorrect in 34% of cases biopsied, many of them involving potentially treatable entities.[131] Among elderly patients with rapidly progressive renal injury, Uezono et al. found 71% of the patients with crescentic GN and 17% with interstitial nephritis. Prebiopsy and histopathologic diagnoses differed in 15% of patients, and both groups benefited from therapeutic intervention.[133]

These data emphasize the value of renal biopsy in the management of AKI of uncertain origin, irrespective of the age of the patient. Accurate diagnosis is important to direct the appropriate treatment, especially in vasculitis and crescentic GN, in which the delay in diagnosis may affect outcome. Given the safety of the ultrasound tomographic-guided renal biopsy, unclear causes of AKI deserve renal biopsy consideration.

Primary Prevention

The development of AKI contributes to dysfunction of other organs, such as heart, lung, brain, and liver.[134–136] Even small changes in GFR are associated with increased mortality.[21] Consequently, primary prevention and early diagnosis of AKI is of central clinical importance. As shown in the conceptual model of AKI illustrated in Figure 28.5, the first step in preventing AKI is an adequate risk assessment. The prevention of AKI should start with assessment of the risk to develop AKI; identification of comorbidities, nephrotoxic medications in use, and early recognition of acute reversible risk factors

associated with AKI. A surveillance approach, applying close monitoring in patients at risk to develop AKI, is a fundamental key to AKI prevention.[137] General preventive strategies are outlined in Table 28.9. A contemporary study has illustrated the potential value of a computerized surveillance system with electronic notification of clinicians to attenuate nephrotoxin-induced AKI.[138] In this study e-mail messages were sent to clinicians to notify them whenever mild increases in SCr occurred in their patients receiving a nephrotoxic drug.[138] This notification led to earlier discontinuation of the offending agent compared to when clinicians were not notified. Earlier notification and cessation of the offending agent decreased the frequency of development of severe AKI from 7.5% to 3.4%. This study confirms that earlier identification of patients with higher risk allows the physician to apply preventive measurements, adjust or suspend nephrotoxic drugs, and, when possible, delay or avoid progression of renal injury. However, recommendations to prevent AKI are not uniformly followed. Weisbord and associates reviewed the medical records of "at risk" patients who underwent radiologic investigations using radiocontrast.[139] They found that of 144 patients eligible for intravenous volume expansion, 16% failed to receive any intravenous fluids. NSAIDs and COX-2 inhibitors were prescribed for 8% of patients.[139] These results validate the effort to bring to light the importance of surveillance, the continuation of the search for earlier markers of AKI, along with providing education to the medical community to valorize small changes in renal function.

28.9 Prevention of Acute Kidney Injury

Avoidance of Nephrotoxicity
- Recognition of agents with nephrotoxic potential
- Recognition of high-risk populations
- Avoidance of concomitant use of more than one nephrotoxin
- Consideration of alternative therapies
- Use of smallest dose and briefest duration
- Formulation/dosing modification
- Monitoring of blood levels if available
- Frequent measurement of renal function
- Surveillance systems to alert clinicians to changes in renal function
- Hydration

Minimization of Nosocomial Infection
- Meticulous handwashing
- Conservative use and rapid removal of intravascular and intravesicular catheters
- Cautious use of antibiotics based on culture data with automatic stop orders to ensure periodic reassessment
- Aspiration pneumonia precautions (elevate head of bed, attention to gastric residual volume, conservative use of sedatives/hypnotics)

Selected Application of Pharmacologic Intervention
- Extracellular fluid expansion
- Maintenance of high urine flow
- Maintenance of cardiac index and mean arterial pressure
- Renal vasodilators
- Intravenous albumin
- Growth factors
- Calcium channel blockers
- Miscellaneous agents

Selected Application of Nonpharmacologic Interventions
- Preoperative optimization
- Maintenance of high oxygen delivery
- Minimization of artificial ventilation
- Supranormal optimization of cardiovascular hemodynamics
- Prophylactic hemofiltration

Risk Assessment

Although AKI associated with one specific cause is common outside the ICU, most critically ill patients have several etiologic factors associated with the development of AKI. AKI acquired in the hospital is often due to a combination of insults. The most common associated causes are failure of renal autoregulation, direct nephrotoxicity, ischemia reperfusion, and inflammatory states. As multiple factors directly influence renal function, the nature and timing of the inciting event is commonly unknown. Accurate identification of AKI risk factors is a fundamental first step in achieving early diagnosis and implementing preventive strategies.

In the ICU population two large prospective observational studies have provided a better understanding of the risk factors associated with AKI in this setting: BEST and PICARD.[10,98] Both BEST and PICARD found sepsis to be the most common contributing factor to ICU-related AKI. A significant percentage of patients developing severe AKI had baseline CKD. In the BEST study in 47.5% of patients ARF was associated with septic shock. Thirty-four percent of ARF was associated with major surgery, 27% was related to cardiogenic shock, 26% was related to hypovolemia, and 19% of ARF was potentially drug-related.[10]

Volume depletion is one of the most common and important risk factors for AKI. In addition to hypovolemia, renal hypoperfusion may be caused by decreased cardiac output, decreased plasma oncotic pressure, hypotension, and decreased renal prostaglandin synthesis. Preexisting renal disease and advanced age, which is often associated with some degree of decreased renal function, are also common risk factors associated with AKI. Administration of a potentially nephrotoxic agent, or drugs that may enhance

nephrotoxicity, obviously increases the risk of AKI. For example, the concurrent use of furosemide and intravenous contrast agents may increase the risk of AKI.[140] Sepsis, congestive heart failure, nephrotic syndrome, and hepatic disease are common conditions associated with AKI.[10]

Although several individual risk factors are associated with the development of AKI, the combination of risk factors and the development of risk stratification scores could provide better tools to predict AKI in specific patient populations (e.g., after cardiac surgery, contrast exposure, hospital-acquired, general surgery, and high-risk surgery).[141–143] Few models have examined the clinical risk factors for the development of AKI among the ICU population.[144,145] Risk profiling can also be used to establish appropriate criteria for surveillance for AKI in hospitalized patients.[146] The use of models to predict the risk of AKI can help clinicians to identify patients with high risk of developing AKI, improve care, and provide better patient counseling.[50]

Volume Expansion

Regardless of the nature of the insult, hemodynamic stabilization with optimization of the cardiac output and blood pressure are key factors in preventing the initiation or worsening of AKI. The general aim is to optimize volume status based on physiologic measurements, maintain adequate hemodynamic status and cardiac output to ensure renal perfusion, and avoid further insults (e.g., hypotension and hypovolemia). Therefore, fluid management is an important intervention for patients in the initiation or extension phase of AKI. However, once the injury is initiated and the extension phase starts, the impact of volume expansion with intravenous fluids on clinical outcomes has not been well described and needs to be balanced with the unwanted consequence of fluid accumulation and overload.

Although there are no specific guidelines for optimizing hemodynamic and fluid status for renal function preservation, extrapolation of data from clinical settings associated with AKI can be instructive. To improve the evaluation of volume status, international guidelines for management of sepsis from the Surviving Sepsis Campaign recommends invasive monitoring with measurements of central venous pressure and venous oxygen saturation (superior vena cava or mixed) based on the early goal-directed therapy approach.[147] The Rivers study randomized patients with severe sepsis or septic shock to receive 6 hours of standard therapy, or 6 hours of early goal-directed therapy, before admission to the intensive care unit. The protocol ensured that all patients had a central venous pressure of between 8 and 12 mm Hg, a mean arterial pressure of >65 mm Hg, and a urine output of >0.5 mL/kg/min, by the administration of 500-mL boluses of crystalloid or colloid and vasopressor agents as necessary. Early goal-directed therapy patients received a central venous catheter capable of measuring $ScvO_2$, and they had to achieve a $ScvO_2$ of >70%, pursued by red blood cell (RBC) transfusion for anemic patients (hematocrit, <30%) and dobutamine therapy for patients above that threshold. This initial approach, applied for 6 hours, reduced the mortality rate, need of mechanical ventilation and vasopressors, and length of hospital stay.[147]

A number of studies have since established the benefits of adequate fluid expansion and earlier vasopressor administration for rapid shock reversal.[148] However, data from recent studies have shown that fluid expansion should be stopped when patients are no longer fluid responsive.[149] Late and prolonged aggressive resuscitation in critically ill patients is associated with fluid overload and worse outcomes. Data from the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network indicate that after initial resuscitation, a conservative approach to fluid administration was associated with faster weaning from mechanical ventilation and decreased length of ICU stay, without any deterioration of kidney function or worse kidney outcomes.[149] A liberal fluid approach as part of early goal-directed therapy appears to be beneficial during the first 6 hours of shock, and a conservative approach should be followed after shock resolution. In AKI patients, in the absence of shock, it is still unknown if these same principles apply. The potential risks of fluid accumulation and volume overload in the setting of AKI need to be considered.[110,150]

Another issue in critically ill patients is determining the optimal fluid to use for resuscitation. The recent Saline versus Albumin Fluid Evaluation (SAFE) trial in 6,997 patients found that fluid resuscitation with saline or albumin resulted in similar relative risks of death in critically ill patients.[151] There were also no significant differences in the proportion of patients with new single-organ and multiple-organ failure, length of ICU stay, length of hospital stay, days of mechanical ventilation, or days of renal replacement therapy.[151] In patients with cirrhosis and spontaneous bacterial peritonitis, intravenous albumin (1.5 g per kg at diagnosis followed by 1 g per kg on day 3) decreased the frequency of AKI (defined as a 50% greater increase in pretreatment BUN or serum creatinine to levels >30 and 1.5 mg per dL, respectively) from 33% to 10% ($P = .002$).[152]

Hydroxyethylstarches (HESs) are the most used nonprotein intravascular volume expanders. In addition to their efficiency in fluid management they have anti-inflammatory properties and reduced cost compared with albumin. However, the physicochemical characteristics and the electrolyte composition of the solvent make these coumponds a potential risk to alter coagulation and platelet function. Another concern with the use of HES is the development of AKI. There is a risk of urine hyperviscosity and consequent tubular lumen obstruction, leading to a tubular lesion called "osmotic nephrosis." The HES solutions have different nephrotoxicty potential depending on the degree of substitution at carbons 2 and 6 in the glucose ring in combination with the molecular weight and molar substitution. They are identified by three numbers which indicate the concentration of the solution; the mean MW (kDa); and, most significantly, the molar substitution (e.g., 10% HES 200/0.5). More recent data using a third generation of HES, 130/0.4, have reported no adverse

effects on renal function in patients who are considered to be at higher risk—for example, those with mild to severe renal dysfunction, advanced age, or on high-dose therapy. In patients at risk for AKI, renal function should be closely monitored when these agents are utilized, and the newer generation of isooncotic HES (130/0.4, 6%) should be preferred.

Prevention of Contrast Medium Nephropathy

Common among the various protocols is the need to establish and maintain an adequate hydration status. To prevent contrast medium nephropathy (CIN) low-risk patients should increase their oral fluid intake and high-risk patients should receive intravenous hydration. Hydration with isotonic saline starting the morning of the procedure, or immediately before in cases of emergency interventions, is superior to half-isotonic (0.45%) saline.[153] A randomized, controlled trial (RCT) compared isotonic saline with isotonic sodium bicarbonate (154 mmol per L $NaHCO_3$ in 5% dextrose) at 3 mL/kg/hr starting 1 hour preprocedure followed by 1 mL/kg/hr for the 6 hours after the procedure. CIN was significantly lower in the bicarbonate group, 2% versus 14% in the saline solution group.[154] The mechanism for the superiority of isotonic bicarbonate over isotonic saline is unclear. Animal studies have shown that bicarbonate is capable of scavenging reactive oxygen species, and the increased pH in the proximal tubule and the renal medulla associated with bicarbonate administration could reduce generation of superoxide. In addition, isotonic saline contains high amounts of chloride with a potential vasoconstrictor effect on renal vasculature. Considering that most hydration studies using isotonic bicarbonate use shorter infusion protocols (only 1 hour) than those using isotonic saline (usually 12 to 24 hours), hydration with bicarbonate is also an attractive alternative in the setting of emergency procedures.

Joannidis et al.[155]conducted a meta-analysis to address discordant results of trials evaluating the efficacy of bicarbonate. Although they confirmed that bicarbonate therapy is more effective in preventing contrast media-induced nephropathy, the study's heterogeneity and publication bias were substantial, preventing clear and definitive conclusions.

Iodinated contrast medium (CM) can be categorized according to osmolality into high-osmolal CM (HOCM; ~2,000 mOsm/kg), low-osmolal CM (LOCM; 600–800 mOsm/kg), and iso-osmolal CM (IOCM; 290 mOsm/kg). Evidence to date suggests that the iso-osmolal, nonionic CM are the least nephrotoxic and should therefore be used in patients at high risk for CIN.

The volume of contrast administered is also a crucial risk factor and an independent predictor of CIN. Based on the volume of contrast given [V] and the creatinine clearance [CrCl], a V/CrCl ratio >3.7 was a significant and independent predictor of CIN in the general population. Administration of contrast more than once in a short period of time is another risk factor, and contrast studies should be postponed at least 48 hours after the last infusion of contrast if possible.

Acetylcysteine

N-acetylcysteine (NAC) is a tripeptide analogous to glutathione able to cross cellular membranes. NAC may reduce vasoconstriction and oxygen free radical generation following contrast administration. Because an increased production of free radicals by the kidneys is partly responsible for their cellular damage in postischemic and nephrotoxic AKI, several clinical studies have attempted to use NAC to prevent or attenuate AKI.

In the first study NAC, a dose of 600 mg orally twice daily the day before and the day of the procedure prevented AKI following radiocontrast administration. Since then there has been ongoing debate as to whether NAC is effective for preventing CIN. Marenzi et al. confirmed the preventive and the dose-dependent effect of NAC in CIN prevention in a large single-center RCT.[156] However, in a large randomized study assessing the efficacy of NAC in preventing CIN (487 patients), intravenous NAC 500 mg did not provide renal protection in patients with impaired renal function compared with placebo.[157] Recent meta-analyses concluded that NAC, compared to periprocedural hydration alone, could lower the risk of CIN in high-risk patients. Therefore, NAC use is recommended based on its potential benefit, low cost, and excellent side effect profile. However, NAC should never replace IV fluids which have a more substantial benefit. In practice, we combine both hydration and NAC in patients at risk for CIN.

Prevention of Drug- and Nephrotoxin-Induced Acute Kidney Injury

Amphotericin B

Amphotericin B (AmB) associated nephrotoxicity can occur in as many as one third of treated patients and the risk of AKI increases with higher cumulative doses. Lipid formulations seem to cause less nephrotoxicity compared with the standard formulation, AmB deoxycholate. Amphotericin lipid complex, liposomal AmB, and AmB colloidal dispersion are significantly less nephrotoxic than amphotericin B deoxycholate; however, there are no conclusions in the comparison of AmB colloidal dispersion nephrotoxicity to other lipid formulations. The use of these formulations can help to preserve renal function in patients with systemic fungal infections; still, they are significantly more expensive. Recently, alternative antifungal agents such as itraconazole, voriconazole, and caspofungin have been more commonly used in patients at high-risk for AKI.

Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor Blockers, and Nonsteriodal Anti-inflammatory Drugs

ACE inhibitors and angiotensin receptor blockers (ARBs) cause vasodilatation of the efferent glomerular arteriole, further reducing intraglomerular pressure already compromised by the blood pressure lowering effect of these agents.

In patients with renal dysfunction they can contribute to reducing the GFR. In patients with an increase in SCr higher than 30% after the initiation of ACE inhibitor and ARB treatment, bilateral renal artery stenosis, stenosis of the renal artery in a solitary kidney, or diffuse intrarenal small vessel disease should be suspected and these drugs should be discontinued. Although there is very limited information it is generaly advisable to discontinue ACE/ARB during an AKI episode. However, these decisions need to be individualized and ACE/ARB may be restarted when there is recovery of renal function in order to support other organ function (e.g., heart failure).

NSAIDs or COX-2 inhibitors should be used with caution in patients with atherosclerotic cardiovascular diseases, CKD, liver disease, and intravascular volume depletion. As NSAIDs cause acute inhibition of cyclo-oxygenase (COX, type I or II), they can reduce GFR and renal blood flow. In critically ill patients, renal hypoperfusion due to decreased effective arterial volume is relatively common, and inhibition of prostaglandin-induced vasodilation by these agents may further compromise renal blood flow and exacerbate ischemic injury.

Aminoglycosides

Clinical evidence of AKI due to aminoglycoside nephrotoxicity usually occurs 5 to 10 days after initiation of the treatment, is typically nonoliguric, and is associated with decreased urine concentrating ability and urinary magnesium wasting. With multiple daily dosing schedules, elevated aminoglycoside peak levels appear to correlate with nephrotoxicity. Because aminoglycoside uptake by proximal tubular cells is a saturable process, once-daily dosing can decrease tubular cell toxicity by reducing the amount of drug taken up by proximal tubular cells. In the general population extended intervals between doses maintains the target dose while decreasing the risk of nephrotoxicity compared with multiple daily dosing. However, intensive care patients have different volumes of distribution and variable clearance, thereby making it difficult to maintain correct serum levels with longer intervals. As these drugs are entirely excreted by glomerular filtration, patients with compromised renal function are at increased risk for nephrotoxicity. In these patients the administration of a large single dose can be associated with a decreased uptake and lower antimicrobial effect.[158] Therefore, to treat serious infections in critically ill patients, dosing with maximum concentration (C_{max}), monitoring, and minimal inhibitory concentration (MIC) evaluation of the pathogen are necessary.[158]

Uric Acid Nephropathy and Tumor Lysis Syndrome

Acute uric acid nephropathy is caused by deposition of uric acid crystals in the interstitium and tubules associated with tumor lysis syndrome (TLS). The early recognition of patients at high risk for TLS is the first step to prevent the development of AKI. In patients with high-grade hematologic malignancies, risk factors for TLS are large tumor burden, lactate dehydrogenase levels above 1,500 IU, extensive bone marrow involvement, and high tumor sensitivity to chemotherapeutic agents. In patients with low or intermediate risk of TLS, allopurinol can be used as a hypouricemic agent and should be started 2 days before chemotherapy. Aggressive hydration with isotonic saline is initiated 2 days before the chemotherapy to maintain a high urinary output, allowing the elimination of uric acid and phosphate. If urinary output decreases despite adequate fluid intakes, a loop diuretic should be added, but renal replacement therapy will be required if oliguria persists.[159] The use of urine alkalinization to promote elimination of urates is not recommended as it can induce calcium phosphate deposition and therefore aggravate TLS. In addition to the hydration, recombinant urate oxidase can reduce uric acid levels and the risk of uric acid deposition nephropathy.[160] Recombinant urate oxidase should be initiated in high-risk patients or for established TLS.

MANAGEMENT OF ACUTE KIDNEY INJURY

After the kidney insult has occurred measures should be directed to avoid further injury, facilitate repair and recovery, and prevent AKI complications (Fig. 28.10). The timing of interventions is crucial to their effectiveness. Various approaches have been applied but are best appreciated in the context of specific scenarios. Initial management includes careful assessment of the etiology of kidney dysfunction and patient volume status. The main goals are maintenance of adequate hemodynamic status to ensure renal perfusion and avoidance of further kidney injury. Appropriate therapeutic interventions to reduce kidney function loss, prevention, and treatment of the associated complications of AKI need to be instituted concurrently. Any potentially nephrotoxic agents should be avoided, including intravascular radiocontrast. Antimicrobial agents such as aminoglycosides, amphotericin, acyclovir, and pentamidine should be avoided or their doses adjusted to avoid further insult.

Fluid and Electrolyte Management

Although early and vigorous resuscitation with crystalloid solutions and aggressive infection control can reduce the incidence of AKI (see previous), the role of fluid resuscitation in established AKI is less clear. Volume status is one of the most difficult parameters to assess and fluid resuscitation should target a predefined preload, stroke volume, or cardiac output rather than a set mean arterial pressure. Many clinical studies have demonstrated the poor value of right atrial pressure and pulmonary artery occlusion pressure in predicting volume expansion efficacy. Other bedside indicators of preload, such as the right ventricular end-diastolic volume (evaluated by thermodilution) and the left ventricular end-diastolic area (measured by echocardiography), have also been shown to be ineffective in differentiating volume

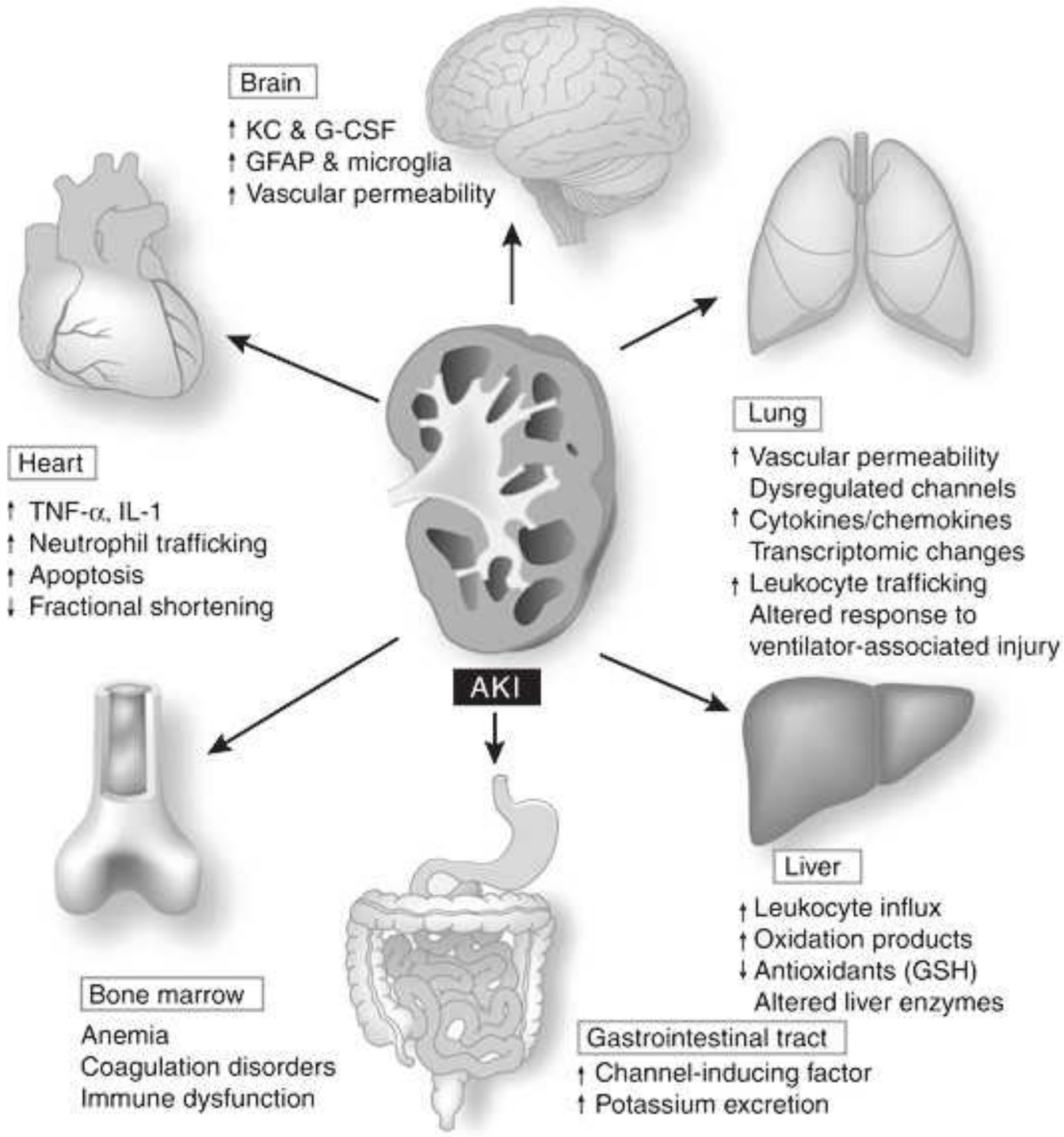


FIGURE 28.10 Acute kidney injury (AKI)-induced distant organ effects. AKI leads to changes in distant organs, including brain, lungs, heart, liver, gastrointestinal tract, and bone marrow. Changes have been described in organ function, microvascular inflammation and coagulation, cell apoptosis, transporter activity, oxidative stress, and transcriptional responses. *AKI*, acute kidney injury; *G-CSF*, granular colony-stimulating factor; *GFAP*, glial fibrillary acidic protein; *GSH*, glutathione; *IL-1*, interleukin-1; *KC*, keratinocyte-derived chemokine; *TNF-α*, tumor necrosis factor-α. (From Scheel PJ, Liu M, Rabb H. Uremic lung: new insights into a forgotten condition. *Kidney Int*. 2008;74(7):849–851.)

responder from nonresponder patients.[161] In critically ill patients receiving mechanical ventilation, respiratory changes in left ventricular stroke volume can predict fluid responsiveness. In hypovolemic patients, positive-pressure ventilation may induce a fall in the venous return and, consequently, in cardiac output. Based on the positive relationship between ventricular end-diastolic volume and stroke volume, the expected hemodynamic response to volume expansion is an increase in right ventricular end-diastolic volume, left ventricular end-diastolic volume, stroke volume, and cardiac output. Because a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume, the increase in stroke volume as a result of end-diastolic volume increase depends on ventricular function.

Volume expansion in critically ill patients can frequently result in a relative increase in body weight of 10% to 15% or more, sometimes doubling the total body water in a short period of time. Some recent studies have demonstrated the role of fluid accumulation on adverse outcomes showing the association between fluid accumulation and mortality and the benefits of restrictive fluid management strategies in acute respiratory distress syndrome (ARDS). A prospective multicenter observational study (PICARD) found that patients with fluid overload, defined as increase in body weight relative to baseline >10%, had significantly higher mortality at 60 days (46% vs. 32%).[110] In addition, increases in the total body water alter the volume of distribution of creatinine resulting in underestimation of serum values.[34] The resulting underestimation of the severity of renal dysfunction may delay recognition and adequate treatment of AKI. In AKI patients presenting with fluid overload the evaluation of kidney function should consider the effect of fluid balance in order to prevent underestimation of AKI severity, correctly modify drug dosing, and avoid use of nephrotoxic agents.

In patients with positive fluid balance, large fluid intakes, and inadequate urine output, loop diuretic therapy can be initiated in conjunction with measures to optimize systemic and kidney perfusion. Although administration of furosemide facilitates fluid management, concerns of possible harm from loop diuretics in AKI surfaced after studies showed that associated diuretic use had an increased adjusted risk of death and nonrecovery of renal function. In urgent situations, morphine and nitrates can be used to alleviate the respiratory symptoms. Morphine reduces patient anxiety and decreases the work of breathing; it can be administered intravenously at an initial dose of 2 to 4 mg over a 3-minute period and can be repeated if necessary at 5- to 15-minute intervals. Nitrates are the most commonly used vasodilators in pulmonary edema. Nitroglycerin reduces left ventricular filling pressure via venodilation and an initial dose of 5 μg per minute of intravenous nitroglycerin is commonly used

in addition to diuretic therapy. When fluid overload cannot be quickly treated with medical management, positive ventilation pressure may need to be initiated with or without endotracheal intubation, and dialysis depends on the clinical situation.

Loop Diuretics and Natriuretics

Although loop diuretics are often prescribed in established AKI,[162] a recent meta-analysis confirmed that their use is not associated with reduced mortality or better kidney recovery.[163] Two prospective cohort studies evaluating diuretic use in AKI and mortality yielded controversial results with one study showing an increase[164] and the other study showing no effect.[165] However, an association between diuretic use and a shorter duration of dialysis was found in this meta-analysis.[163] Still, two other meta-analyses have shown that loop diuretics do not affect mortality, need for dialysis, or number of dialysis sessions required.[166] In regard to morbidity, diuretics are associated with an increased risk of ototoxicity.[166] Concomitant prescription of aminoglycosides and diuretics should be avoided due to an increased risk of ototoxicity. Well-designed trials of diuretics are required to assess their benefits and potential side effects in AKI. In the meantime, we suggest that a trial of diuretics may be utilized to enhance urine output; however, if this approach is not successful, escalating doses of diuretics should be avoided.

Atrial natriuretic peptide (ANP) has been studied as a treatment for AKI in four RCTs.[45,167–169] ANP was shown to reduce need for dialysis but did not reduce mortality.[45] In the largest study published so far, ANP improved overall dialysis-free survival in the subgroup of oliguric patients.[167] A subsequent trial, including 222 oliguric patients, did not confirm that ANP reduces mortality or dialysis-free survival.[169] The most recent study evaluated the use of ANP treatment for a mean of 5.3 ± 0.8 days in 61 patients who underwent cardiac surgery. The use of ANP decreased the probability of dialysis and improved dialysis-free survival.[168] Larger studies are required to confirm the benefits of ANP in AKI.

Nesiritide, a B-type natriuretic peptide, is currently approved by the FDA for the treatment of heart failure. Nesiritide induces vasodilation and indirectly increases cardiac output, having no inotropic or heart rate effect. In some individuals, a resultant decrease in the neurohormonal activation can result in natriuresis and diuresis. In adults with acute decompensated heart failure, nesiritide reduces pulmonary capillary wedge pressure, reduces right atrial pressure and systemic vascular resistance, decreases symptoms of heart failure, and enhances clinical status. However, questions regarding the risks of nesiritide therapy have recently been raised. The most frequently reported adverse effect is dose-related hypotension and an acute increase in SCr concentration. This effect in kidney function has not been shown to negatively affect mortality and reviews of large, observational, registry databases do not suggest an adverse inpatient mortality effect compared with other vasodilator therapies.[170]

Vasoactive Agents

"Renal-dose" dopamine (0.5 to 3 μg/kg/min), given as a specific vasodilatator to increase renal blood flow and prevent AKI, does increase urine output but does not affect AKI outcome or mortality.[171] Dopexamine, a synthetic dopamine analogue, is a dopamine 1 and less potent dopamine 2 receptor agonist. Small studies performed in patients undergoing liver transplant surgery have not found a beneficial effect of dopexamine in preventing AKI.

No RCTs have assessed the effect of norepinephrine on prevention of AKI. In a meta-analysis, fenoldopam, a dopamine receptor-1 agonist increasing blood flow to the renal cortex and outer medulla, was shown to reduce the risk of AKI in postoperative or critically ill patients (odds ratio, 0.43).[172] A large RCT will need to be performed to confirm these findings. Intrarenal administration of fenoldopam allows the use of a substantial dose of fenoldopam mesylate while avoiding systemic adverse effects such as hypotension. In a registry of 268 patients treated with intrarenal fenoldopam, infused for at least 1 hour, the incidence of CIN was less than 1%, compared to 27% based on historic rates in that population. Although we are still waiting for additional studies to confirm these results, it may be a promising preventive measurement for patients at high risk of CIN.

Vasopressors are often considered to be detrimental for organ perfusion. However, experimental and clinical data suggest a beneficial effect of norepinephrine on the urine output in sepsis. A small prospective study including 14 patients in septic shock showed that norepinephrine improved SCr and creatinine clearance when mean arterial pressure was raised above 70 mm Hg.[173] However, in a small RCT including 28 patients, increasing mean arterial pressure from 65 to 85 mm Hg with norepinephrine did not improve renal function.[174]

Fenoldopam has shown improved outcomes in some studies. In a recent meta-analysis, fenoldopam decreased the need for dialysis (7% vs. 10%) and in-hospital mortality (15 vs. 19%) in ICU patients.[172] However, this meta-analysis had limitations, such as no standardized criteria for initiation of dialysis, heterogeneity of populations and AKI definitions, dosage and duration of treatments, and the absence of independent measure of GFR. An adverse effect of fenoldopam is hypotensive episodes, and it may be more frequent and deleterious outside RCTs.[172,175] These results show that, although widely promoted, the use of fenoldopam needs to be confirmed with an adequately powered trial.

Avoidance of Hyperglycemia

Effective management of hyperglycemia in critically ill patients has been a major topic of discussion since a landmark study demonstrated a significant reduction in mortality and morbidity in surgical patients who were treated with an intensive regimen to control blood glucose. Subsequent studies have highlighted the importance of hyperglycemia for adverse outcomes in various populations and proposed algorithms

for glycemic control. A systematic review of intensive insulin therapy in critically ill patients found a 38% reduction in the incidence of AKI, whereas other negative trials showed no benefit and an increased risk of hypoglycemia.[8]

In critical illness membrane expression of GLUT-1, GLUT-2, and GLUT-3 proteins is upregulated and allows glucose to enter cells more in proportion to extracellular glucose levels. This contributes to glucose overload in several tissues, including brain neurons, hepatocytes, endothelial cells, and renal tubules. These events are associated with various cytokines (tumor necrosis factor α [TNF-α] and interleukin 6 [IL-6]), hormones (cortisol, catecholamines, and growth hormone), and other molecules (vascular endothelial growth factor and transforming growth factor [TGF]) that are also upregulated in renal failure.

The kidney plays an important role in glucose homeostasis. In humans renal glucose production contributes approximately 25% to systemic glucose production, whereas renal glucose uptake accounts for 20% of systemic glucose removal. Because glucose homeostasis in the kidney is regulated by insulin, loss of kidney metabolic function could account for a component of insulin resistance as a result of loss of a major target organ for insulin action. Uremia is also associated with decreased hepatic and peripheral glucose uptake and a reduction in peripheral tissue glucose transporters. The kidney also metabolizes insulin and reduced renal function prolongs the half-life of insulin and can contribute to hypoglycemic events. One of the major risk factors for development of hypoglycemia in the ICU is the presence of preexisting renal dysfunction and the need for kidney replacement therapy.

Some studies have shown that maintaining blood glucose levels around 110 mg per dL reduced the onset of acute kidney injury from 12.3% to 9% ($P = .04$) and need for dialysis by 41%. Whereas the lowered blood glucose level was related to reduced mortality and other complications, the insulin dosage was an independent determinant for prevention of AKI.[176] Two large intervention studies in medical and surgical ICU patients confirmed a similar association and found that the development of newly acquired AKI decreased by 75% and 45%, respectively.[177] In a large observational study, patients who did and did not have diabetes and required glycemic control had more infections, anemia, and AKI (11% and 7% versus 4%; $P < 0.001$) compared with control subjects.[178] Additional observational studies from different populations suggest a linkage of hyperglycemia and the metabolic syndrome with the development of AKI. Most of these studies used a doubling of creatinine or a creatinine level >2.5 mg per dL as a criterion for AKI; however, a more sensitive criterion (0.5 mg per dL creatinine change) would likely increase the incidence of AKI. Whether these associations are simply a consequence of the deranged metabolic milieu that accompanies critical illness or there is a direct effect of hyperglycemia and insulin resistance on the kidney still needs more evaluation.

Although several pieces of the puzzle linking hyperglycemia and kidney function are still missing, there is enough evidence now to suggest that the kidneys are active in the process and a target for new injury. On the basis of these conclusions hyperglycemia should be considered a major risk factor for AKI in the ICU and should prompt specific measures. Clinicians should seek out a history of hyperglycemia as part of the evaluation of critically ill patients who are at risk or develop AKI and institute preventive and therapeutic measures.

However, achieving glycemic control is not easy and hypoglycemic events are commom in AKI patients. In a recent large, international, randomized trial in critically ill patients (NICE sugar study), intensive glucose control increased the absolute risk of death to 90 days compared to conventional glucose control. Severe hypoglycemia was significantly more common with intensive glucose control. In a meta-analysis including 26 trials, a total of 13,567 patients, and data from the NICE sugar study, the relative risk (RR) of death with intensive insulin therapy compared with conventional therapy was 0.93. Patients in surgical ICUs presented a benefit from intensive insulin therapy (RR 0.63), whereas patients in medical ICU did not (RR 1.0).

Based on these recent studies it appears that intensive insulin therapy significantly increased the risk of hypoglycemia and is not associated with a benefit in mortality among critically ill patients. Whether there is a benefit in preventing or ameliorating AKI is still unclear. We would recommend maintaining appropriate control of blood glucose in the 120 to 140 mg per dL range.

Protective Mechanical Ventilation

Mechanical ventilation is associated with the disruption of pulmonary epithelium and endothelium, lung inflammation, atelectasis, hypoxemia, and the release of inflammatory mediators.[179,180] These inflammatory mediators can cause injury to lungs and other organs.[181] Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 mL per kg of body weight and may cause stretch-induced lung injury in patients with acute lung injury.[182,183] Treatment with a ventilation approach designed to protect the lungs from excessive stretch resulted in improvements in several important clinical outcomes in patients with acute lung injury and ARDS.[183] Thus, in mechanically ventilated patients an important preventive measure is to avoid excessive lung stretch during adjustments to mechanical ventilation, and a lower tidal volume protocol should be used in patients with acute lung injury and ARDS.

Mechanical ventilation has been shown to be an important independent factor for mortality in AKI patients, and the time on mechanical ventilation is also associated with increased mortality.[10] In addition, AKI is a risk factor for prolonged mechanical ventilation.[184] Patients with prolonged mechanical ventilation are predisposed to pulmonary infections, and infection is the leading cause of death in patients with AKI.

In patients in need for renal support, removal of fluid with ultrafiltration can improve pulmonary edema resulting in better oxygenation.[122] However, in these patients, remov-

ing fluid faster than interstitial fluid can be mobilized into the circulation can induce hypotension and contribute to prolonged AKI. A judicious rate of fluid removal should be individualized to the clinical status of the patient in order to avoid this vicious cycle.

Pharmacologic Approaches

A variety of drugs are effective in altering the course of experimental models of ATN. However, only a few have consistently shown benefits in preventing or attenuating established AKI (Table 28.10).

Statins

Statins induce downregulation of angiotensin receptors, decrease endothelin synthesis, decrease inflammation and improve endothelial function by inhibiting nuclear factor κB, decrease expression of endothelial adhesion molecules, increase nitric oxide bioavailability, attenuate production of reactive oxygen species, and protect against complement-mediated injury. All of these mechanisms may be involved in the protective effect against CIN. A number of publications support the potential for kidney protection with statin administration.[185] A recent prospective study evaluated the effect of statins to decrease the incidence of CIN during percutaneous coronary intervention. Patients receiving statins prior to the procedure had a significant decrease of CIN (3% vs. 27%).[186] However, in a retrospective cohort study evaluating patients undergoing major vascular procedures,[187] perioperative statin administration did not improve renal function, reduce length of stay, or reduce mortality. No benefit was observed in patients with a preexisting creatinine clearance <40 mL per min. Currently, there is no basis to recommend the initiation of statin therapy specifically for the pericontrast period to prevent CIN. Patients who are already on statin therapy, or need it for other indications, should be maintained on statins through contrast procedures.

Calcium Channel Blockers

Calcium antagonists have been shown to reverse the afferent arteriolar vasoconstriction induced by a variety of stimuli and also have an independent natriuretic effect.[188] These drugs were exhaustively evaluated in the prevention of AKI, especially in the context of transplant-associated nephropathy. If administered prophylactically calcium blockers protected against posttransplantation delayed graft failure in some studies. However, a large multicenter RCT evalu-

28.10 Drugs Tested in Clinical Studies for Prevention or Treatment of Acute Kidney Injury

Drugs	Results
Prevention	
Dopamine	No effect on kidney function
Fenoldopam	Controversy: no effect on kidney function or beneficial effect on kidney function
Loop diuretics	No effect on kidney function
N-acetylcysteine	Variable beneficial effect in contrast-induced nephropathy
Statins	Beneficial effect on kidney function
Calcium channel blockers	No effect on kidney function
Adenosine antagonists	Controversial effect on kidney function
Multipotent stem cells	Beneficial effect on kidney function in Phase 1 studies
Erythropoietin	Uncertain based on a large Phase 2/3 trial in intensive care unit patients
Small interfering ribonucleic acid	Beneficial effect on kidney function, undergoing Phase 2/3 trials
Treatment	
Loop diuretics	No effect
Atrial natriuretic peptide	Possible beneficial effect on survival and kidney function
Dopamine	No effect on mortality or kidney function
Norepinephrine	Possible beneficial effect on kidney function
Fenoldopam	Controversy: No effect on mortality or kidney function Beneficial effect on mortality and need for dialysis
Insulin	Controversial effect
Mesenchymal stem cells	Beneficial effect on kidney function
Erythropoietin	Beneficial effect on kidney function
Alkaline phosphatase	Beneficial effect on kidney function

ating the effect of isradipine on renal function, incidence and severity of delayed graft function, and acute rejection after kidney transplantation did not find any benefit.[189] A systematic review evaluated the benefits and harms of using calcium channel blockers in the peritransplant period in patients at risk of ATN after cadaveric kidney transplantation.[190] The authors suggested calcium channel blockers given in the perioperative period reduced the incidence of ATN posttransplantation. However, the heterogeneity of the trials makes the comparison of studies difficult. The use of calcium channel blockers during renal transplant surgery may be of benefit in extended donor criteria transplants (e.g., donors older than 60 years, predonation SCr level higher than 1.5 mg per dL, cerebrovascular disease as the cause of death), or those with prolonged ischemia times.

Adenosine Antagonists

Small clinical studies evaluating the role of theophylline, an adenosine antagonist, in the prevention of contrast nephropathies have shown discordant results. A recent study, including seven RCTs, concluded that the prophylactic administration of theophylline or aminophylline appeared to protect against CIN.[191] However, this meta-analysis included studies that did not control for hydration status. A recent RCT adding theophylline to NAC showed a reduced incidence of CIN. Additional selective blocker agents, such as rolofylline, have maintained renal function in patients with decompensated heart failure, although they have not been assessed for prevention of AKI. At the moment it remains unclear if theophylline as a solo agent might be useful in preventing contrast nephropathy. Further studies are necessary prior to its routine use.

Disorders of Electrolyte and Uric Acid Metabolism

Hyperkalemia, hyponatremia, metabolic acidosis, and hyperuricemia often occur in AKI.

Potassium

A rise in plasma potassium concentrations to >5.5 mEq per L is a frequent complication seen in 50% of patients with AKI. Hyperkalemia is due to continued potassium release from cells, or dietary potassium, in the face of impaired renal potassium elimination. The potassium concentration of intracellular water is about 155 mEq per L in skeletal muscle. Thus, in conditions such as tumor lysis syndrome and rhabdomyolysis, dangerous levels of hyperkalemia can occur quickly. In patients with rhabdomyolysis induced by extensive traumatic muscle crush injury, plasma potassium concentrations can rapidly increase from normal to life-threatening levels. Other factors including a cellular shift of potassium due to academia; hyperosmolality or potassium loads from exogenous sources such as blood, dietary intake, potassium salts (e.g., salt substitutes); or large doses of penicillin G can also contribute to hyperkalemia. AKI induced by NSAIDs can also be associated with marked hyperkalemia. The effect of these agents in suppressing renin and aldosterone secretion may be responsible in part.

The primary risk of hyperkalemia is on cardiac conduction where it may cause bradycardia or asystole. If echocardiogram (ECG) changes are present, the administration of intravenous calcium is urgent. Concomitantly, sources of oral or intravenous potassium should be identified and removed, including drugs with effect on potassium handling such as beta-adrenergic antagonists, potassium-sparing diuretics, ACE inhibitors, ARBs, and other drugs that inhibit renal potassium excretion.

The next step is to enhance the shift of potassium to the intracellular space using parenteral glucose and insulin infusions. The onset of action is within 20 to 30 minutes, and the effect lasts for 2 to 6 hours. Continuous infusions of insulin and glucose-containing intravenous fluids can be used to prolong their effect. Sodium bicarbonate also promotes shift of K^+ into the intracellular space, the effect occurs in less than 15 minutes, and has 1 to 2 hours' duration. This therapy can be started if there is no concern of fluid overload (44.6 mEq intravenously over 5 minutes); however, the potassium-lowering effect of sodium bicarbonate is most prominent in patients with metabolic acidosis. Beta-adrenergic agonists given as aerosols are also effective but more likely to produce side effects and so are not often prescribed to treat hyperkalemia.

Potassium excretion should be increased by the administration of loop diuretics and cation exchange resins, such as Kayexalate or calcium resonium. The resins can be administered orally or rectally, as a retention enema. In case of hyperkalemic emergencies, rectal administration is preferred, as the colon is the major site of action of this drug. If hyperkalemia is unresponsive to conservative measures, or occurs in patients with ESRD, emergency hemodialysis is the treatment of choice. As it may take some time to initiate RRT, medical management should always be used while waiting for dialysis to be started. Monitoring for potassium levels should continue following conservative or dialytic management to prevent and treat rebound hyperkalemia from the underlying process.

Acid-Base Disorders

In AKI, metabolic acidosis is the most common acid-base abnormality. The metabolic acidosis results from continued production of nonvolatile acid and decreased renal ability to excrete acid. In severe catabolic states, the usual daily production of 1 mEq per L of nonvolatile acid can be markedly increased. Accumulation of phosphate and unexcreted unmeasured anions—such as sulfate, urate, hippurate, hydroxypropionate, furanpropionate, and oxalate—are contributory. Hypoalbuminemia can attenuate this acidification process, and it is exacerbated by lactic acidosis. Despite retention of unmeasured anions, the anion gap remains within

normal limits in 50% of patients. Although metabolic acidosis is frequent, triple acid-base disturbances can also occur.

The approach to acid-base disturbances in AKI needs to be adjusted to the underlying causes. There is controversy surrounding the optimal treatment of acute metabolic acidosis. When metabolic acidosis is simply a complication of AKI, sodium bicarbonate can be administered if the serum bicarbonate concentrations fall below 15 to 18 mmol per L. Bicarbonate administration in lactic acidosis due to an underlying shock is controversial given the possibility of an increase in CO_2 generation, worsening of the intracellular acidosis, and volume overload. Rapid improvement in the metabolic status may also enhance hypocalcemia, which may lower cardiac output. Therefore, since the benefit of bicarbonate in patients with lactic acidosis due to an underlying shock seems limited, most physicians would restrict the administration of sodium bicarbonate to patients with severe metabolic acidosis (arterial pH below 7.10 to 7.15) to maintain the pH above 7.15 to 7.20 until the primary process can be reversed. Alternative forms of base treatment have not been studied extensively in patients with AKI. Tris(hydroxymethyl)aminomethane (THAM) is excreted in the urine and its clinical efficacy compared to sodium bicarbonate remains unproven.[192] We do not recommend its use in patients with AKI, especially in patients with hyperkalemia, because THAM does not decrease potassium levels in contrast to bicarbonate and can even cause hyperkalemia. Restriction of protein intake has also been suggested as a method of acidosis control since protein breakdown has been associated with worsening acidosis.

Sodium

Hyponatremia is a common complication of AKI and is caused by an absolute or relative increase in solute-free water intake. Rare associations with hyponatremia and AKI include toxin ingestion,[193,194] rhabdomyolysis, infection,[195] and hypothyroidism.[19] The treatment consists of water restriction to below the level of output. Salt restriction is usually necessary to treat fluid overload and/or edema. In cases of true volume depletion with associated prerenal AKI, isotonic saline will need to be administered to correct both disorders.

Intensive care patients with hypernatremia are more prone to AKI. In most cases, treatment of the underlying cause will be necessary and water deficit will need to be estimated. Water should be administered orally or intravenously as dextrose in water to correct serum sodium at a maximum rate of 10 mmol/L/day. Dialysis and continuous RRT, in particular, may be required to optimally correct sodium disorders in AKI.

Renal Replacement Therapy

The issues regarding RRT in AKI are currently the source of much debate and investigation. The areas of debate include when to initiate, what modality to use, and the dose of therapy to deliver.

Dialysis Initiation

Whether or not to provide dialytic support, and when to initiate, are two of the fundamental questions facing nephrologists and other intensivists in most cases of severe AKI. The optimal timing of dialysis for AKI is not defined. The association of early initiation of dialysis with survival benefit was first suggested by case series with historical controls conducted in the 1960s and 1970s.[197–199] However, the relevance of these studies to current practice is questionable, given that BUN concentrations at the start of dialysis in the "early" treatment groups in these previous studies are considered high by modern standards. In the modern dialysis era, few studies have examined the association of the timing of initiation of dialysis in AKI with mortality. Moreover, changes in illness severity, especially in later years, make comparisons of studies extremely difficult. Single-center studies that were restricted to AKI after trauma[200] and coronary artery bypass surgery[201,202] suggested a benefit to dialysis initiation at lower BUN concentrations. In a broader population, Bouman et al.[203] randomized 106 critically ill patients with AKI to early versus late initiation of dialysis. The early initiation group started dialysis within 12 hours of low urine output, less than 30 mL per hour for 6 hours, not responding to diuretics or hemodynamic optimization, or creatinine clearance less than 20 mL per minute. The late initiation group started dialysis when classic indications were met. The study did not find differences in ICU or hospital mortality between the groups of early and late initiation, or in renal recovery among survivors. A prospective multicenter observational cohort study[204] performed by the Program to Improve Care in Acute Renal Disease (PICARD) analyzed dialysis initiation—as inferred by BUN concentration in 243 patients from five geographically and ethnically diverse clinical sites. Survival rates were slightly lower for patients who started dialysis at higher BUN concentrations, despite a lesser burden of organ system failure. Adjusting for age, hepatic failure, sepsis, thrombocytopenia, and serum creatinine and stratified by site and initial dialysis modality, initiation of dialysis at higher BUN was associated with an increased relative risk for death (95% CI, 1.16 to 2.96).

Although the maintenance of BUN concentrations below arbitrarily set levels is usually a reference for starting dialysis treatment, BUN reflects factors not directly associated with kidney function such as catabolic rate and volume status. SCr is influenced by age, race, muscle mass, catabolic rate, and its volume of distribution varies on fluid overload patients. Thus, neither creatinine nor BUN should be used to absolutely determine when to initiate dialysis. In a prospective multicenter observational study conducted at 54 intensive care units (ICUs) in 23 countries,[205] timing of RRT was stratified into "early" or "late" by median urea at the time RRT started and also categorized temporally from ICU admission into early (less than 2 days), delayed (between 2

and 5 days), or late (more than 5 days). Timing by serum urea showed no significant difference in mortality (63.4% for urea ≤24.2 mmol per L vs. 61.4% for urea >24.2 mmol per L). However, when timing was analyzed in relation to ICU admission, late RRT was associated with greater crude mortality (72.8% late vs. 62.3% delayed vs. 59% early, P = .001) and covariate-adjusted mortality (OR, 1.95; 95% CI, 1.30–2.92; P = .001). Overall, late RRT was associated with a longer duration of RRT and stay in hospital and higher rate of dialysis dependence.

There are potential safety concerns regarding earlier initiation of dialysis, including increased risk for infection from an indwelling dialysis catheter, hypotension, delayed renal recovery, and leukocyte activation from contact with dialysis membranes.[206,207] The concept that dialysis initiation would prolong the course of AKI was supported by experimental data showing renal lesions consistent with fresh ischemia in dialyzed animals without systemic hypotension, long after their initial renal injury. In the presence of ischemia, the vasculature of normal kidneys responds with vasodilation as part of the autoregulatory response to maintain renal blood flow and GFR. In ATN, autoregulation is impaired; as a result, recurrent ischemic tubular injury is more likely to occur, thereby delaying the restoration of function. However, it is difficult to document that earlier initiation of dialysis is harmful because patients with more severe forms of renal injury may develop indications for dialysis earlier in their ICU course and may be more likely to develop irreversible disease independent of therapy. Several factors can influence the survival and recovery of renal function in dialytic AKI patients. Whether these risks outweigh the potential benefits of earlier initiation of dialysis is still unclear.[207]

In current practice the decision to dialyze is based most often on clinical features of volume overload and biochemical features of solute imbalance (e.g., azotemia, hyperkalemia). Data from an RCT comparing IHD to CRRT suggest that the indication for dialysis is an important determinant of outcome.[208] In that study patients dialyzed predominantly for solute control experienced better outcomes than those dialyzed predominantly for volume overload. Patients dialyzed for control of both azotemia and volume overload experienced the worst outcome. Volume resuscitation is a common strategy used in the treatment of multiorgan failure, particularly when accompanied by sepsis syndrome and hypotension. It is often applied indiscriminately in the setting of oliguric AKI, where it is assumed that providing additional volume will improve renal perfusion, prompting correction of renal dysfunction. Although this may be of great benefit to patients with prerenal azotemia, excessive volume administration can lead to pulmonary edema, compromising oxygenation and ventilation, and hastening the need for dialysis. In critically ill patients, especially in the postoperative period and in septic patients after volume expansion, the increase in total body water can reach more than 10 L within 7 days.[149,209] Mukau et al.[210] found that 95% of their patients with postoperative AKI had fluid excess of more than 10 L at the time of dialysis.

Despite recent evidence suggesting positive fluid balance as possibly harmful for ICU patients, the association between fluid balance and outcomes in AKI patients is not completely defined. These patients are expected to present higher positive fluid balance; however, the impact in the prognosis is poorly understood. Payen et al.[211] analyzed data from the Sepsis Occurrence in Acutely Ill patients (SOAP) study, a multicenter observational cohort study including 198 ICUs. In AKI patients, mean daily fluid balance was significantly more positive among nonsurvivors than survivors (0.98 ± 1.5 versus 0.15 ± 1.06 L per 24 hours, P <0.001). Bouchard et al.[150] found that fluid overload, defined as a >10% increase in body weight relative to baseline, was associated with significantly higher mortality rates at 60 days (46% vs. 32%; P = .006). The adjusted odds ratio for death associated with fluid overload at dialysis initiation was 2.07 (95% CI, 1.27–3.37). In that study, among the dialyzed patients, survivors had lower fluid accumulation at dialysis initiation compared with nonsurvivors (8.8% vs. 14.2% of baseline body weight) (Fig. 28.11).

These factors collectively suggest the need to develop evidence-based, patient-specific, and nonbiased indications for the initiation of dialysis in AKI (Table 28.11). Timing of RRT, a potentially modifiable factor, might exert an important influence on patient survival. However, it largely depended on its definition. We favor utilizing an approach that recognizes that the strategy in treating AKI is to minimize and avoid uremic and volume overload complications. Thus, it is not necessary (and arguably harmful) to wait for progressive uremia to initiate dialytic support. The indications for dialysis should include a consideration of the need for renal support (as well as renal replacement), and the timing of dialysis should be based on the goals to be achieved.

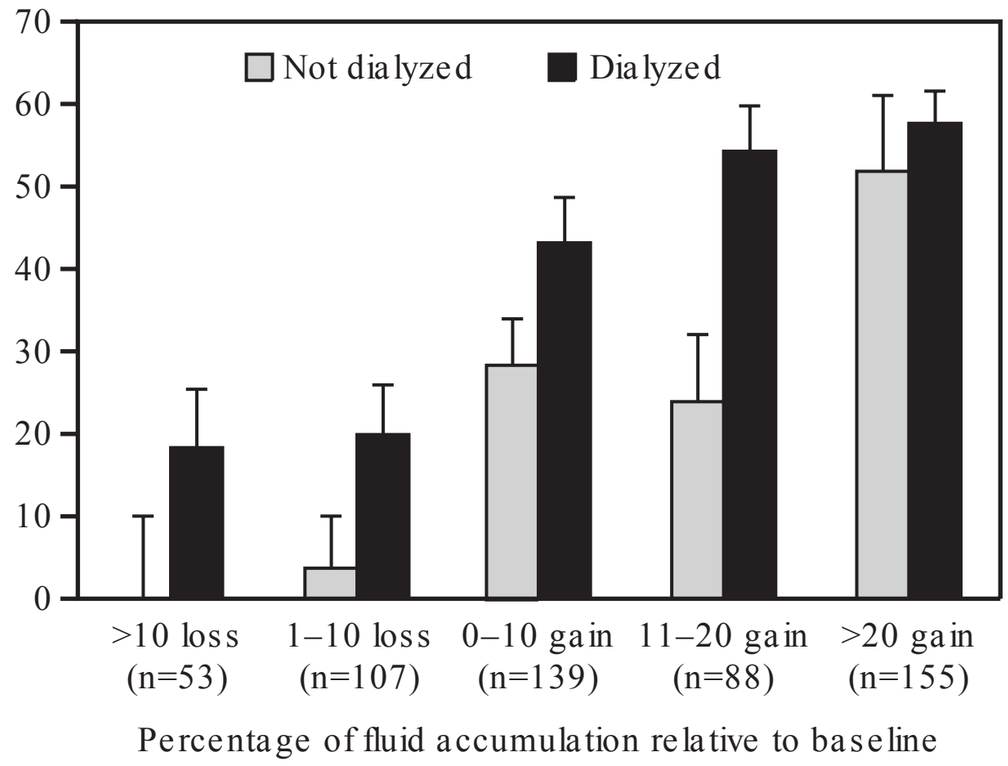


FIGURE 28.11 Mortality rate by final fluid accumulation relative to baseline weight and stratified by dialysis status. (From Bouchard J, Mehta RL. Fluid accumulation and acute kidney injury: consequence or cause. *Curr Opin Crit Care*. 2009;15(6):509–513.)

28.11 Prognostic Factors in Acute Kidney Injury

Severity of Renal Dysfunction
- Magnitude of rise in serum creatinine concentration
- Urinalysis
- Fractional excretion of sodium
- Presence of oliguria or anuria
- Requirement for renal replacement therapy
- Duration of renal dysfunction

Underlying Health of the Patient
- Age
- Presence of chronic kidney disease
- Presence, severity, and reversibility of underlying disease

Clinical Circumstances
- Cause of the renal failure
- Severity and reversibility of acute process(es)
- Number and type of other organ systems failed
- Development of sepsis and other complications

Intermittent Versus Continuous

The choice of intermittent or continuous therapy is currently based on the experience of the nephrology team and the availability of therapies. When both therapies are available, the indication of CRRT or IHD is based on the patient's neurologic, hemodynamic, and catabolic status. Ideally, the therapy should be tailored to the patient's demands, which changes daily in the critically ill. It is now accepted that more than one therapy will be utilized for managing patients during the course of AKI. Transitions from CRRT to IHD are common and reflect the changing needs of patients during their AKI course. For instance, patients in the ICU may initially start on CRRT when they are hemodynamically unstable, transition to SLED-EDD when they improve, and leave the ICU on IHD. In the recent ATN trial, 57% of the patients had more than one therapy whereas 23% and 20% had IHD and CRRT alone.[212] We recommend that all therapies should be utilized as indicated to best support patient needs through their course.

The comparison of the operating characteristics of the two therapies will help to recognize the strengths and weaknesses of each modality. Fluid removal is a desirable component of any renal replacement therapy and is a major goal of renal replacement for AKI.[213] Fluid removal and, hence, fluid balance, is limited to the period of dialysis. If the patient is hemodynamically unstable during this period, it may be difficult to remove any fluid. Fluid removal is slower and hypotension is uncommon with peritoneal dialysis and CRRT. It has been suggested that the latter modality may be associated with an improved outcome, due perhaps to more stable hemodynamics; however, this has not been rigorously demonstrated.[207] The high efficacy of these therapies in continuous fluid removal allows for use in situations other than renal failure, such as heart failure.[214] Pediatric patients are better suited for PD and CRRT, and these modalities have been used successfully in the management of AKI in neonates.[215,216]

The continuous removal of fluid permits the delivery of optimal nutrition as fluid load becomes a nonlimiting factor. Two other factors influence the overall nutritional balance of the patient in dialysis: the composition of the dialysate and hemofiltrate solutions. Although lactate-based dialysate and hemofiltrate solutions can rarely result in hyperlactatemia and worsening of acid-base status, they can cause higher urea generation rates compared to bicarbonate solutions.[217,218] The content of glucose in dialysate solutions results in glucose absorption during the dialysis procedure, which contributes to the caloric load. This glucose content is also associated with an increase in endogenous insulin secretion in most patients, and some patients may require exogenous insulin.[219] The use of a lower dextrose concentration-based dialysate in CRRT usually prevents this complication. Another nutritional factor is the dialysance of amino acids, vitamins, and trace elements across the filter. Losses appear to depend more on the serum levels than on the underlying clinical status of the patient.[220] To avoid potential harm, vitamin supplementation should be provided for all patients on CRRT regardless of dialysis dose, and pharmacists should be consulted to optimize drug dose adjustments.[221] With the massive expansion of therapeutic alternatives in critical care (especially antibiotics), much more research is required to understand optimal drug during CRRT.

The effect of the dialysis modality on outcome is still a major question to be answered. In four prospective cohort studies,[222–225] none suggest differences in mortality between modalities. A recent systematic review[226] identified nine RCTs that compared CRRT versus intermittent methods.[227–234] The relative risk of death associated with CRRT was not significantly different than with intermittent hemodialysis (RR 1.10; 95% CI, 0.99–1.23). The last Cochrane Review comparing dialysis modalities concluded that, in hemodynamically stable patients, modality does not appear to influence outcomes. In hemodynamically unstable patients, CRRT may be preferable as patients on CRRT maintain higher mean arterial pressure and show a trend toward lesser need for escalation of vasopressor therapy and arrhythmias.[235]

Dose of Dialysis

Until recently, dialysis dose was considered to play a pivotal role in improving outcomes in critically ill patients requiring CRRT. The relationship between treatment dose and patient outcome in AKI was first investigated prospectively in a single-center study where 425 subjects were randomized to 45, 35, and 20 mL/kg/h of postdilution continuous venous-venous hemofiltration (CVVH). Subjects receiving doses of

45 and 35 mL/kg/h experienced lower mortality rates compared to subjects receiving 20 mL/kg/h, 42% and 43% versus 59%, respectively ($P < 0.005$). After this study was published, three other RCTs showed contradictory results. Bouman et al.[203] found no difference in mortality among subjects who received higher hemofiltration volumes—48.2 mL/kg/h versus 19.5 mL/kg/h. Tolwani et al.[236] randomized 200 patients for CVVHDF using two different ultrafiltration volumes. The intensive group received 29 mL/kg/h against 17 mL/kg/h for those in the standard group. There was no significant difference in the mortality rate between groups: 64% versus 60% ($P = .56$). Adding a diffusive component (18 mL/kg/h of dialysate) in 206 patients submitted to hemofiltration (25 mL/kg/h of replacement fluid), Saudan et al.[237] showed a significant decrease in mortality—46% versus 61% ($P = .0005$). In this study, subjects in the hemodiafiltration group received substantially more overall solute clearance than subjects in the hemofiltration group, making it difficult to determine if the reduction in mortality was attributable to the higher dose or the addition of diffusive clearance.

Schiffl et al.[238] conducted an RCT comparing conventional alternate day dialysis to daily dialysis among 160 patients with AKI, assessing 14-day survival. The groups were similar with respect to baseline characteristics and illness severity and were analyzed by intention to treat. In the daily group, the weekly delivered Kt/V was 5.8 ± 0.4, and in the conventional group it was 3.0 ± 0.6. The duration of therapy was 3.3 hours per session in the daily group and 3.4 hours per session in the conventional group. The daily HD group had improved survival (28% vs. 46%, $P = .01$) and recovered kidney function more quickly (9 ± 2 days vs. 16 ± 6 days, $P = .001$). Factors significantly associated with an increased odds of death included alternate day HD (vs. DHD) (OR 3.92, 95% CI, 1.68–9.18, $P = .002$), higher APACHE III scores (OR 1.06, 95% CI, 1.01–1.12 per point increase, $P = .02$), oliguria (OR 3.02, 95% CI, 1.35–6.77, $P = .007$), and sepsis (OR 3.27, 95% CI, 1.43–7.50, $P = .005$).[238] The Schiffl study was the first randomized trial suggesting that patients with AKI benefited from more frequent HD and, consequently, a higher weekly Kt/V.[238]

Two recent large multicenter RCTs did not find benefit of intensive dose of dialysis over a standard dose.[212,239] The ATN trial was a randomized multicenter study including 1,124 critically ill AKI patients with sepsis or at least one nonrenal organ dysfunction. This trial aimed to provide a definitive conclusion on the benefits of intensive versus less-intensive dialysis dosage.[212] Intensive dosage was defined as CRRT with an effluent rate of 35 mL/kg/h, IHD or SLED six times per week, and less-intensive dosage as CRRT with an effluent rate of 20 mL/kg/h, and IHD or SLED three times per week. Each IHD or SLED treatment was aimed to achieve a single-pool Kt/V_{urea} of 1.2 to 1.4. The mean delivered dosages (5.4 treatments per week vs. 3 treatments per week at Kt/V of 1.3 or effluent rate of 35.8 vs. 22.0 mL/kg/h) were almost identical to the prescribed dosages. Subjects were switched from one modality to another according to their Sequential Organ Failure Assessment (SOFA) cardiovascular score (IHD when the score was 0 to 2 and CRRT or SLED when the score was 3 or 4). Baseline characteristics were similar between the groups. There were no differences in the primary endpoint, mortality at 60 days, in the duration of renal replacement therapy, or rate of recovery of kidney function or nonrenal organ failure between the groups. In contrast to the Bouman and Tolwani studies,[203,236] the sample size of the ATN study was sufficiently large so that there was adequate power to detect modest differences in mortality.

In the RENAL study 1,508 critically ill adults meeting predetermined criteria for the initiation of RRT were randomly assigned to postdilution CVVHDF with an effluent flow of 40 mL/kg/h or 25 mL/kg/h.[239] All patients received CRRT as their first mode of RRT and only 7% of patients received IHD later in their ICU stay. Thus, the RENAL study constitutes a more direct measure of the relationship between intensity of CRRT and survival.

The design of the ATN or the RENAL studies did not include predetermined strategies for some parameters that may have influenced the results, such as the timing of initiation of therapy, fluid balance, and site of delivery of replacement fluids (pre- vs. postdilution). It is important to note that subjects in the less intensive group received more renal replacement therapy than most patients in routine clinical practice. Therefore, practitioners should not conclude that dose is unimportant. In AKI there is a marked discrepancy between prescribed and delivered dose of dialysis. The delivered Kt/V in AKI patients have been shown to be 30% lower than prescribed,[238,240] resulting from hypotension, dialyzer clotting, and vascular access recirculation.[241]

The ideal dialysis prescription for AKI should incorporate an assessment of the dose of dialysis delivered. Unfortunately, there are no standard methods for assessing the dose of dialysis in AKI. In ESRD, the dose of dialysis prescribed and delivered is usually based on an assessment of the amount of urea removed, using urea kinetic modeling either via direct dialysis quantification or by using regression formulas incorporating fractional urea reduction.[242] A key feature of these methods is the assumption that patients with ESRD are in steady state with respect to urea generation, volume status, and renal and extrarenal clearance. However, dialysis dosing in AKI needs to account for highly variable body water volumes and varying urea generation rates, as well as different methods of dialysis and changes in renal and extrarenal clearance. Unfortunately, these issues have not been accurately quantified or adequately studied in prospective cohort studies or clinical trials conducted to date.

In general, the dose of dialysis is based on modality-specific criteria (e.g., membrane choice, operational characteristics, and the duration of each dialysis session). For patients treated with IHD, the frequency of dialysis is another determinant of the overall dose of dialysis delivered. Table 28.3 shows a comparison of the factors affecting dose of dialysis for IHD and CRRT. Several investigators have attempted to quantify the dose of dialysis delivered in AKI

using methods used for patients with ESRD. Clark et al.[243] compared IHD to CRRT techniques using a computer model to derive the required IHD frequency (per week) or required CRRT for a given patient weight for desired BUN values of 60, 80, and 100 mg per dL. For the attainment of intensive IHD metabolic control (BUN = 60 mg per dL) at steady state, a required treatment frequency of 4.4 dialyses per week was predicted for a 50-kg patient. However, the model predicted that the same degree of metabolic control could not be achieved even with daily IHD therapy in patients 90 kg or more. On the other hand, for the attainment of intensive CRRT metabolic control (BUN = 60 mg per dL), required urea clearance rates of approximately 900 mL per hour and 1,900 mL per hour were predicted for 50 and 100 kg patients, respectively. These data suggest that, for many patients, rigorous control of azotemia equivalent to that readily attainable with most CRRT programs can be achieved with intensive (nearly daily) IHD regimens only. In practice, the frequency of dialysis usually depends on the patient's clinical and biochemical status. It is noteworthy that reimbursement policies in the United States currently do not support the practice of daily IHD.

Other promising concepts should also be prospectively tested to improve our current understanding of the pathophysiology of AKI and help to better define dialysis dosage requirements. To improve the definition of dialysis dosage, other dialysis parameters, such as fluid balance, need to be assessed. In CRRT the effluent volume per se may not accurately reflect clearance as clotting of filter is associated with declining efficacy in effluent saturation. Although current RRT substitute small solute and volume clearances, the later parameter has never been included in randomized studies on dialysis dosage in AKI.[211,212,239] More importantly, fluid excess has been shown to be independently associated with increased mortality in one adult and several pediatric observational studies in AKI.[101,211,215] Fluid excess was usually defined as a proportion of initial hospital admission weight. In the largest pediatric study, the percentage fluid excess at dialysis initiation was significantly lower in survivors versus nonsurvivors (14.2 ± 15.9% vs. 25.4 ± 32.9%; $P < .03$) even after adjustment for severity of illness.[101] Therefore, fluid excess may contribute to imbalances between groups and should be better characterized in future studies. Results from the ongoing RENAL trial, a multicenter trial comparing an augmented versus a normal CRRT regimen, may add additional insight into the question of dialysis dose and outcome (Fig. 28.12).

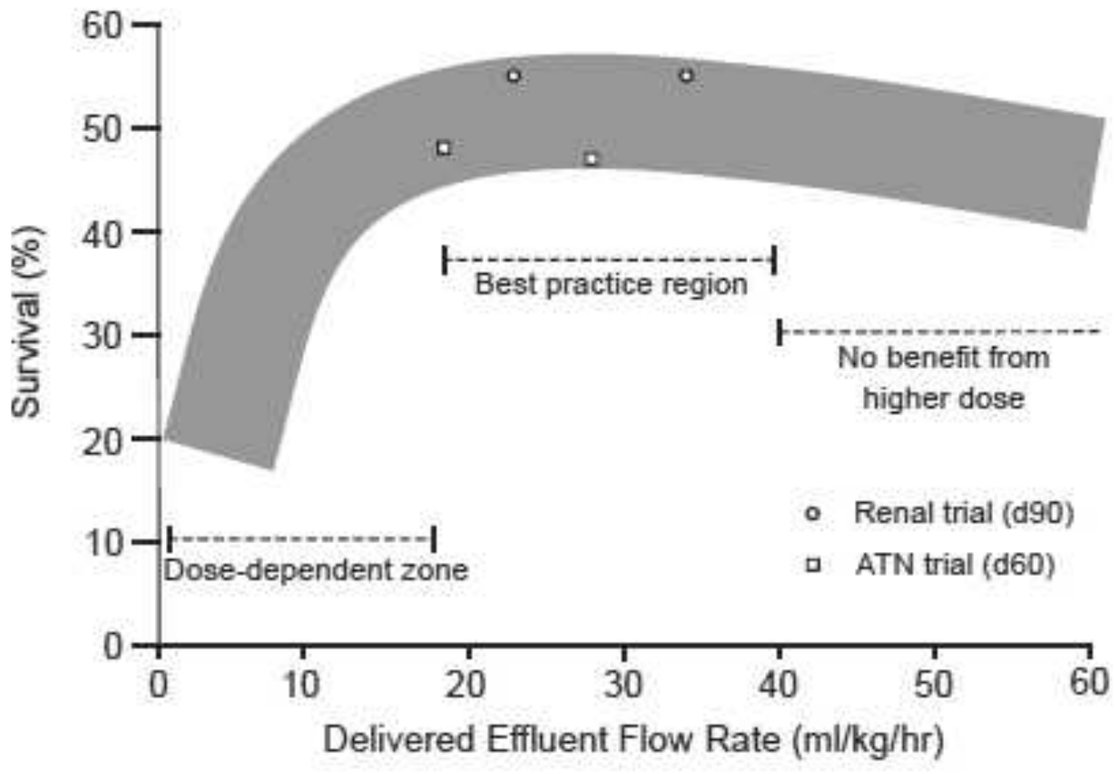


FIGURE 28.12 Possible relationship between delivered dose of continuous renal replacement therapy and survival, with results from the ATN and RENAL. These studies indicate a plateau response at the dose ranges examined. Acute tubular necrosis (ATN) doses are corrected for predilution. To reproduce these results, clinicians will need to prescribe continuous renal replacement therapy doses above the lower target dose in the trial protocols (20 or 25 mL/kg/min) as larger periods of filter downtime can be expected outside a clinical trial environment. Below this best-practice region, survival is likely to be dose-dependent; however, the exact nature of this relationship has not been formally determined. Doses above the best-practice region are unlikely to be beneficial to unselected patients and could potentially be harmful. *ATN*, Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network; *RENAL*, Randomized Evaluation of Normal versus Augmented Level. (Adapted from Prowle JR, Schneider A, Bellomo R. Clinical review: Optimal dose of continuous renal replacement therapy in acute kidney injury. *Crit Care*. 2011;15(2):207.)

Nutritional Considerations

AKI patients present an increased risk of protein–energy malnutrition due to poor nutrient intakes and high catabolic rates. Nutritional support should be directed to ensure adequate nutrition, prevent protein–energy wasting with its concomitant metabolic complications, promote wound healing and tissue repair, support immune system function, accelerate recovery, and reduce mortality.

In critically ill patients, the metabolic response to stress causes increased production of some cytokines (IL-1, IL-6, TNF-α), counterregulatory hormones (catecholamines, cortisol, glucagon), and immune mediators (thromboxane A2, prostaglandin F2a, prostaglandin E2).[244] The activation of stress-mediated response causes skeletal muscle breakdown, impairs amino acid transport into skeletal muscles, suppresses insulin-mediated protein synthesis, depletes body energy reserves and constitutive proteins, and increases urea production and peripheral insulin resistance.[245] As a result, critically ill patients have loss of body energy reserves (glycogen, protein, and fat stores), hypertriglyceridemia, hyperglycemia, and negative nitrogen balance.

Severe malnutrition occurs in up to 42% of patients with AKI. Severely malnourished patients have a significantly increased in-hospital length of stay, increased risk for comorbidities (sepsis, septic shock, hemorrhage, intestinal occlusion, cardiac dysrhythmia, cardiogenic shock, acute respiratory failure), and increased in-hospital mortality.[246] Nutritional assessment is difficult, especially in AKI patients

presenting higher metabolic demands. Subjective Global Assessment (SGA) accesses nutritional status, requires no additional laboratory testing, and is highly predictive of outcome.[247]

Patients with AKI should receive a basic intake of at least 1.5 g/kg/day of protein and an energy intake of no more than 30 kcal nonprotein calories or 1.3 × BEE (Basal Energy Expenditure) calculated by the Harris–Benedict equation. Thirty to 35% of calories should come from lipid, as lipid emulsions. Monitoring of nitrogen balance to assess the effectiveness of supplemental nutritional therapy is determined by measuring protein intake over 12 or 24 hours and urinary excretion of urea nitrogen over the same time interval. A positive or negative protein balance is used to determine the adequacy of protein intake of the patient. It is calculated as follows:

$$\text{Nitrogen balance} = (\text{protein intake}/6.25) - (\text{UUN} + 4),$$

Protein intake and urinary urea nitrogen (UUN) are each expressed in grams.

The enteral route should be the first choice for nutritional support if the gastrointestinal tract is functioning, whereas parenteral nutrition should be reserved when the gastrointestinal tract cannot be used, or when the enteral route appears inadequate to reach nutrient intake goals.[248] AKI itself and other factors commonly present in critically ill patients, such as medications, hyperglycemia, and electrolyte disorders, can impair gastrointestinal motility.

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